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Tandem Aza[4+2]/Allylboration: A Novel Multicomponent Reaction for the Stereocontrolled Synthesis of α-Hydroxyalkyl Piperidine Derivatives

And

N,N-Diethanolaminomethyl Polystyrene: An Efficient Solid Support to Immobilize Boronic Acids.

by

Jyoti M. Tailor ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

Department of Chemistry

Edmonton, Alberta

Fall, 2000

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Degree: Master of Science

Year of Degree Granted: 2000

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Date. September 13, 2000.

To my Husband Mukesh Tailor

ABSTRACT

The discovery of novel chemical reactions or reaction sequences allowing the generation of useful chemical products may be regarded as the heart of organic chemistry. Herein, a novel tandem aza[4+2]/allylboration reaction is described. This tandem multicomponent reaction includes a diene, a dienophile, and an aldehyde reacting in one-pot to afford polysubstituted α-hydroxyalkyl piperidine derivatives. A diverse number of compounds can be obtained since the reaction allows for the incorporation of four independent variable substituents in one reaction.

1-aza-4-borono-1,3-butadienes (**19**, page 19) represent a novel class of heteroatom-containing dienes with several useful properties. These dienes can be easily prepared by the acid-catalyzed condensation of aldehyde **39**, made using a modified literature procedure, with the desired hydrazines (Scheme 11, page 29). This protocol has been found to be quite general for the preparation of various dienes containing different hydrazone substituents.

The [4+2] cycloaddition of 1-aza-4-borono-1,3-butadienes with dienophiles proceeds with complete *endo*-selectivity, and the subsequent allylboration step produces two new stereogenic centers in a single relative

configuration. Although the products are obtained in modest yields, four stereogenic centers are obtained in one step. Another attractive feature of these dienes is the possibility for asymmetric induction by introducing a chiral auxiliary. Indeed, a chiral (S)-(-)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine (SADP)-derived diene **66b** was reacted with *N*-phenylmaleimide and benzaldehyde to provide bicycle **67b** in >95% diastereomeric excess (page 56).

This new multicomponent reaction is potentially useful towards the synthesis and screening of combinatorial libraries, and as a strategy for the total synthesis of alkaloids containing a hydroxyalkyl side chain at the α-position of the piperidine ring.

ACKNOWLEDGMENTS

I would like to express my utmost gratitude to Professor Dennis G. Hall for his support, guidance and encouragement throughout the journey of my research work. I really appreciate all his interest and assistance in the preparation of this thesis.

I would also like to pass my gratitude to the technical staff of the Chemistry Department at the University of Alberta for the great services. I appreciate the great work done by Dr. T. Nakashima for the crucial NMR determinations and Dr. R. McDonald for trying so hard to get the X-ray crystal structure. I would also like to thank members of the Hall's group from bottom of my heart for helping and guiding me throughout my research work and special thanks to Kim Thompson, Dave Manku, Jason Kennedy and Michel Gravel for proofreading and correcting my thesis. I am also thankful to Richard Wilson (BioChem Pharma) for his fruitful discussions.

Last but not the least, I would like to thank my family. I could not have done this without their moral support, specially my husband Mukesh Tailor.

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List of Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
APT	Attached Proton Test
Anal.	elemental analysis
br	broad
Boc_2O	*tert*-butoxycarbonyl anhydride
Bn	benzyl
°C	degree Celsius
CBH	catecholborane
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
^{13}C NMR	Carbon-13 nuclear magnetic resonance
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
2D	two dimensions
d	days
d. e.	diastereomeric excess

DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DME	1,2-Dimethoxyethane
EDG	electron-donating group
ES	electrospray
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethyl ether
equiv	equivalent
EWG	electron-withdrawing group
FMO	frontier molecular orbital
Fmoc	9-Fluoromethyl chloroformate
g	gram(s)
h	hour(s)
^1H NMR	Proton nuclear magnetic resonance
H_2O	water
HOMO	highest-occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared

J	coupling constant
$LiAlH_4$	lithium aluminum hydride
LUMO	lowest-occupied molecular orbital
m	multiplet
M^+	molecular ion
MCR's	multicomponent reactions
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole
mp	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NaOAc	sodium acetate
NaOH	sodium hydroxide
NOE	Nuclear Overhauser enhancement
PG	protecting group
Ph	phenyl
Ph_3P	triphenylphosphine

ppm	parts per million
PS	polystyrene
psi	pounds per square inch
R	alkyl group
Ra-Ni	raney nickel
RAMP	(R)-(+)-1-amino-2-(methoxymethyl)pyrrolidine
rt	room temperature
s	singlet
SADP	(S)-(-)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine
SAMP	(S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMAO	trimethylamine *N*-oxide dihydrate
UV	ultraviolet

Chapter One

Tandem Aza [4+2] / Allylboration: A Novel Multicomponent Reaction for the Stereocontrolled Synthesis of α-Hydroxyalkyl Piperidine Derivatives.

I. INTRODUCTION

i) Multicomponent reactions (MCR's) and their potential application in the synthesis of α-hydroxyalkyl piperidine derivatives.

Chemical reactions that use more than two starting materials at once are called multicomponent reactions (MCR's).[1] In the light of chemical productivity and the generation of molecular diversity, an "ideal" MCR should involve as many simple and cheap components as possible. The starting materials should be different and all or most of the atoms of the starting materials should be incorporated into the final product in order to optimize atom economy.

MCR's are well suited for natural product synthesis and combinatorial library applications as the products are formed in a single step and diversity is achieved by simply varying each component.[2] There are very few examples of MCR's in the literature and only one for the preparation of piperidine derivatives described by P. A. Grieco.[3] Grieco has developed a method where iminium ions derived from aryl amines and aldehydes in the presence of cyclopentadiene, giving rise to piperidine derivatives **4** (Figure 1).

There is no MCR available for the production of cyclic β-amino alcohols like α-hydroxyalkyl piperidines. The method described by Petasis for the synthesis of acyclic β-amino alcohols involves a one-pot three-component reaction of an organoboronic acid (**5**), an amine (**6**), and an α-hydroxy aldehyde (**7**) (Figure 2).[4] β-Amino alcohols are useful building blocks for a large variety of bioactive compounds, such as protease enzyme inhibitors.[5] Synthetic routes for the construction of β-amino alcohols often involve multiple steps, harsh experimental conditions or allow only limited types of substituents. In contrast, the products from MCR's are formed in a single step and diversity can be achieved by introducing different R groups.

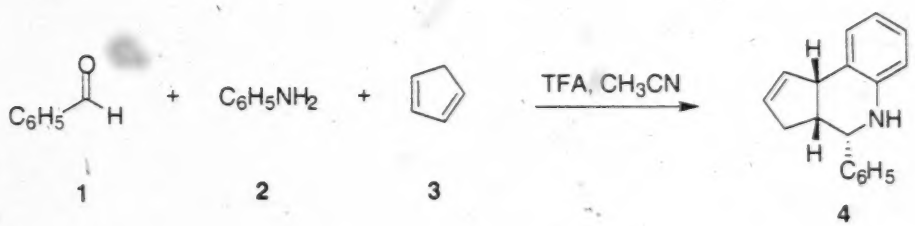


Figure 1. Formation of piperidine derivatives.

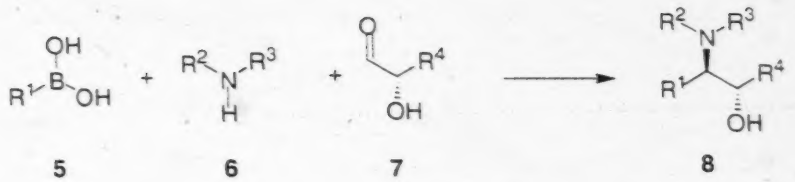
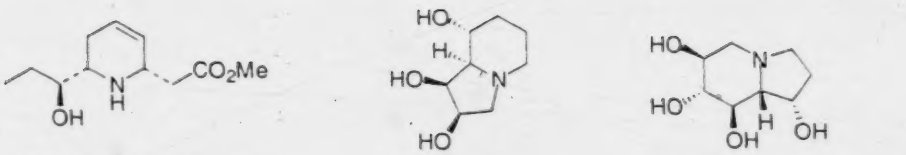


Figure 2. One-pot synthesis of acyclic β-amino alcohols.

Piperidine, pyrrolizidine, and polyhydoxylated indolizidine alkaloids embody a β-amino alcohol unit and are endowed with a vast range of biological activities.[6] Several of these alkaloids (e.g. methyl palustramate, swainsonine and castanospermine) have shown to be potent glycosidase inhibitors (Figure 3). Castanospermine (+) is a powerful inhibitor of both α and β-D-glucosidase enzymes.[7] These enzymes are involved in a number of processes such as digestion, the biosynthesis of glycoproteins and the catabolism of glycoconjugates. Inhibition of glycosidases has shown remarkable therapeutic potentialities in the treatment of metabolic diseases. This increasing interest in glycosidase inhibitors has recently led to an impressive number of synthetic routes to access such compounds and structural variants thereof.[6,7] The synthetic stereochemical control of the β-amino alcohol unit in pyrrolizidines and indolizidines represents a challenge to organic chemist.



(-)-Methyl palustramate Swainsonine (+)-Castanospermine

Figure 3. Some examples of piperidine derivatives containing a β–amino alcohol unit.

We realized that a tandem hetero[4+2]/allylboration reaction could be very useful as a stereocontrolled method to construct diverse α-hydroxyalkyl piperidine ring systems. In this thesis, we describe our approach to α-hydroxyalkyl piperidine derivatives, based upon the one-pot tandem [4+2]/allylboration reaction shown in Scheme 4 (page 19). The [4+2] cycloaddition of 1-aza-4-borono-1,3-butadienes with the appropriate dienophiles followed by the addition of the intermediate cycloadducts to aldehydes gives the final allylboration products.

ii) Diels-Alder reaction.

The Diels-Alder reaction is extremely valuable for the construction of carbocyclic rings in organic synthesis. In one step, a cyclohexene ring and two new carbon-carbon bonds are formed, and

the stereochemistry as well as regiochemistry can be controlled by the proper choice of reactants. The stereochemistry of the Diels-Alder reaction can be considered from four different aspects:

(a) *cis*-principle

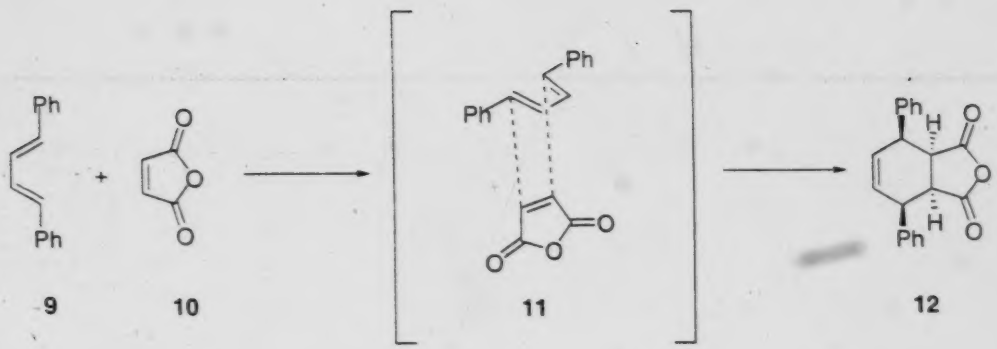
With respect to the dienophile, the addition is stereospecifically *syn* because of the frontier molecular orbital (FMO) overlap requirements in the Diels-Alder transition state, with few exceptions.[8] In the terminology of orbital symmetry classification, the Diels-Alder reaction is a $[_{\pi}4_{s}+_{\pi}2_{s}]$ cycloaddition - an allowed process. The subscript π indicates that π electrons are involved in the cycloaddition and s is used to designate *suprafacial* geometry. There are two possible ways to form bonds to the two atoms of a π bond, or to the two terminal atoms of a set of conjugated π bonds. The two new bonds may be formed either from lobes on the same side of the π bond system or from lobes on opposite sides. Woodward and Hoffmann designated addition to lobes on the same side of a π system as *suprafacial* addition and called addition to lobes on opposite sides of a π system *antarafacial* addition (Figure 4).

Suprafacial sites *Antarafacial* sites

Figure 4. *Suprafacial* and *antarafacial* sites.

The transition state for a concerted reaction requires that the diene adopt the *s-cis* conformation. The diene and dienophile approach each other in an approximately parallel plane. This approach can be illustrated by the reaction of *trans,trans*-1,4-diphenyl-1,3-butadiene (**9**) with maleic anhydride (**10**) to give the adduct **12** stereospecifically (Scheme 1). Furthermore, with respect to the 1,4-disubstituted diene, this reaction is stereospecific and *syn* as indicated in Scheme 1. Thus, both the two ring junction hydrogens and the two-phenyl groups are *cis* to each other in the product **12**.

Scheme 1

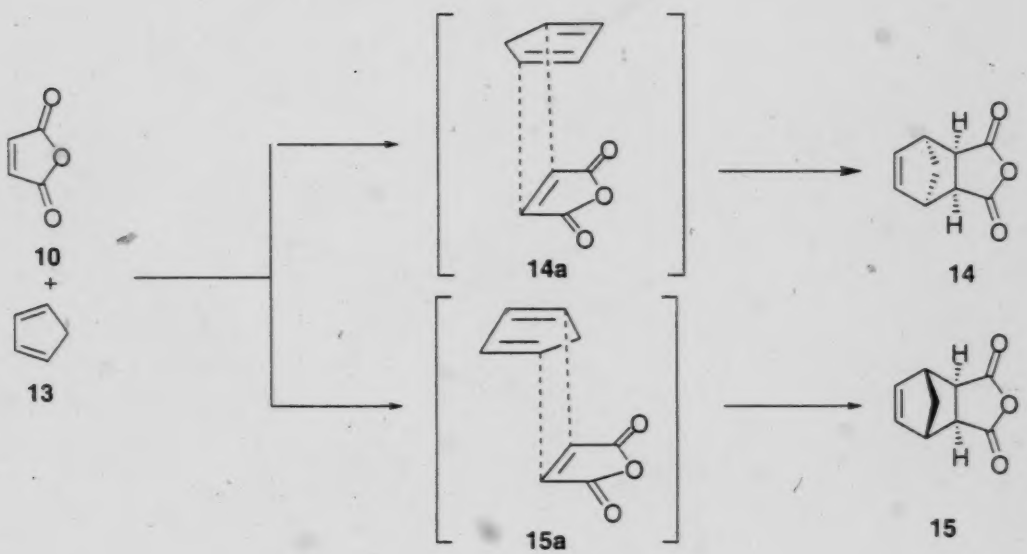


(b) The *endo*-rule

The *endo* rule was originally formulated for additions of cyclic dienes and dienophiles to predict which of the two possible transition states, **14a** or **15a**, would be favored (Scheme 2). The most stable transition state arises from the *endo* orientation in which there is 'maximum accumulation of double bonds'. In the addition of maleic anhydride to cyclopentadiene, two different products, namely the *exo* and the *endo*, might be formed depending on the manner in which the diene and the dienophile are disposed in the transition state. This preference can be explained in terms of secondary orbital overlap between the π system of the diene and the directing substituent(s) of the dienophile. In the *endo* transition state **14a**, the referenee

substituent on the dienophile **10** is oriented towards the π orbital of the diene **13** leading to the overlap of the orbital between these two π systems. In the *exo* transition state **15a**, the substituent is oriented away from the π system. Therefore, there is no secondary orbital overlap.

Scheme 2



(c) The *ortho* and *para* rules

In a Diels-Alder reaction between unsymmetrical dienes and dienophiles, without counting stereoisomers, there are two possible

products with different regiochemistry (Figures 5 and 6). Although mixtures are often obtained, usually one regioisomer is predominant. This preference can be understood in terms of frontier orbital theory. In most cases, the dienophile bears an electron-withdrawing group (EWG) and the diene an electron-donating one (EDG). In this, the main interaction in the transition state arises between the highest occupied molecular orbital (HOMO) of the diene and the lowest-occupied molecular orbital (LUMO) of the dienophile. The orientation of the product is influenced by the size of the atomic orbital coefficients at the termini of the respective conjugated systems. As shown in Figure 5, the coefficient at C-4 is larger than the coefficient at C-1 in the HOMO of the diene bearing an electron-donating substituent at C-1 and and the coefficient at C-2 is larger than the coefficient at C-1 in the LUMO of the dienophile bearing an electron withdrawing substituent. The carbons having the largest coefficient in the two frontier orbital will begin the bonding process. It turns out that in most cases it leads mainly to the 1,2 ('*ortho*') adduct with 1-substituted dienes (Figure 5). For example in the reaction of 1-diethylaminobutadiene and ethyl acrylate, the '*ortho*' adduct **16** is formed preferentially.

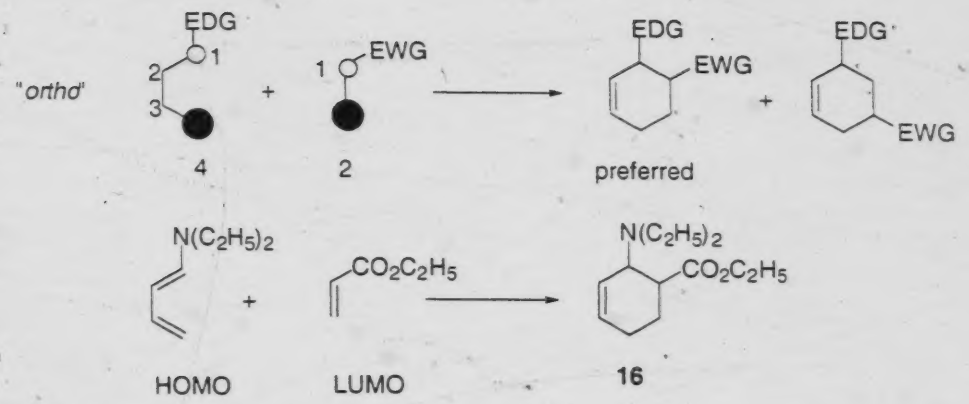


Figure 5. "*ortho*" rule.

In Figure 6, the coefficient at C-1 is larger than the coefficient at C-4 in the HOMO of the diene bearing electron-donating substituents at C-2. Thus, the preferred adduct will be that in which the two substituents are in a *para* position. For the reaction of 2-ethoxybutadiene and methyl acrylate, the formation of the '*para*' adduct **17** is indeed preferred.

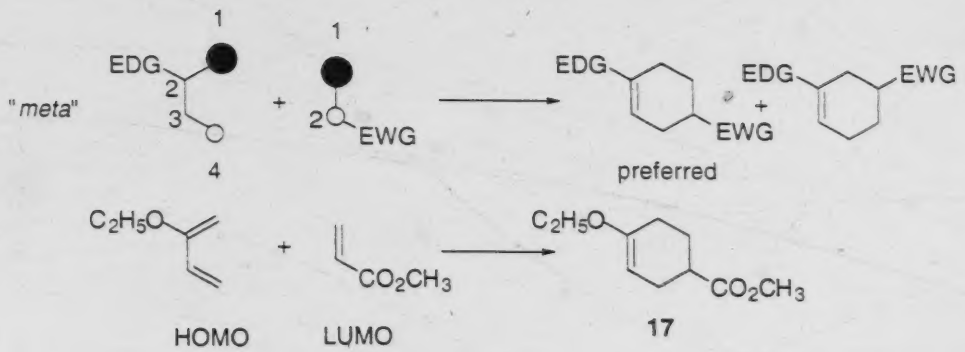
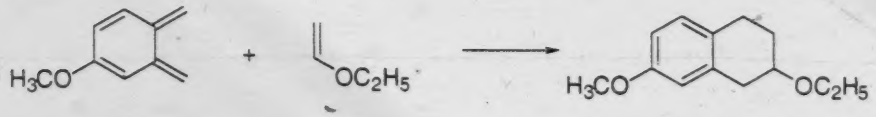


Figure 6. "*para*" rule.

When substituents on both the diene and the dienophile are electron donating, the favoured product should be that with a *meta* orientation of the substituents (**18**).



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(d) *Cisoid* diene requirement

Figure 7. *Cisoid* diene conformation.

Molecules with double bonds in a *cis* relationship around the single (s) bonds connecting the double bonds are said to be in *s-cis* form (Figure 7). The *s-cis* conformation of the conjugated diene is required by the geometry of the transition state in the Diels-Alder reaction. This conformation may be obtained from dienes, which have been either frozen into the *cisoid* conformation (as in a ring), or which are able to achieve it during the reaction by rotation about the σ bond (as in an acyclic diene).[9]

Bulky substituents, which discourage the diene from adopting the *cisoid* conformation, hinder the reaction. For example, 2-*t*-butyl-1,3-butadiene is 27 times more reactive than butadiene. However, 2,3-di-*t*-butylbutadiene is completely unreactive. This difference in reactivity is explained in Figure 8. The bulky *t*-butyl substituent prefers the *s-cis* conformation as it releases steric hindrance in the molecule. The presence of a *t*-butyl substituent on both C-2 and C-3, however, prevents attainment of the *s-cis* conformation.

Figure 8. Effect of bulky substituents on the rate of Diels-Alder reaction.

If the diene is frozen into the *transoid* conformation, the reaction does not take place. Some investigations have shown that cyclic dienes, which have the frozen cisoid confirmation usually, react faster than the corresponding open-chain compounds.

(e) Electronic factors

The 'normal' Diels-Alder reaction takes place between an electron-rich diene and an electron-deficient dienophile. The most commonly encountered substituents for the 'normal' Diels-Alder reaction are COR, CO_2R, CN and NO_2 and the dienophile, which contains one more of these groups in conjugation with a double or triple bond, react readily with dienes. α,β-Unsaturated carbonyl compounds are reactive dienophiles. However, there are number of Diels-Alder reactions that involve an electron-rich dienophile and an electron-deficient diene. These are known as inverse electron demand Diels-Alder reactions.

iii) Hetero-Diels-Alder reaction.

In principle, the Diels-Alder reaction should also be useful for the construction of heterocyclic compounds. For instance, the

reaction of a diene and a dienophile in which one of the carbon atoms of the π system has been replaced by nitrogen would result in a six membered unsaturated nitrogen heterocycle (*i.e.* a piperidine ring). Dienes possessing heteroatoms capable of donating their electron density into the conjugated π-system are known to display high reactivity in various [4+2] cycloaddition reactions. The accepted rationale for this phenomenon, in accordance with the frontier molecular orbital (FMO) theory, is that the electron-rich heteroatoms increase the energy level of the diene's HOMO. This perturbation decreases the energy difference between the diene's HOMO and the dienophile's LUMO, resulting in a greater stabilization of the transition state, which is reflected in a higher reaction rate. Hetero-Diels-Alder reactions are gaining widespread acceptance as useful tools in heterocyclic synthesis. Among the most common heterodienes are the 1-azadienes used in the preparation of piperidine derivatives (Figure 9).

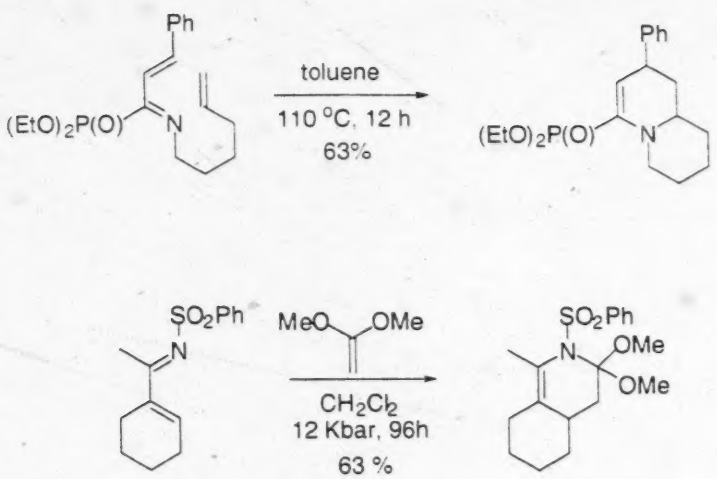


Figure 9. The aza Diels-Alder adducts.

However, 1-azadienes are less reactive than many other heterodienes due to the combined effects of three factors. First, *s-cis-s-trans* conformational equilibrium and imine-enamine isomerism lead to a low concentration of the reactive species.[10] Second, the reaction is less thermodynamically favourable than the all carbon dienes because of the relative weakness of the carbon-nitrogen single bond in the product as compared to the starting imine. The σ-bond strengths for ethane and methylamine are 85.8 and 84.8 kcal/mol respectively, whereas the π-bond strengths for ethylene and methylene imine have been calculated to be 59.4 and 74.3 kcal/mol respectively. Finally, the electron density of the diene often makes it unreactive. The latter factor is crucial and has led to the development of two kinds

of 1-azadienes, namely those bearing electron-withdrawing groups on the nitrogen and therefore suitable for Inverse Electron Demand Diels-Alder reactions, and those bearing electron-donating groups on the nitrogen atom, which can be used in 'normal' electron-demand reactions. The first class of compounds is represented by the unstable 1-acyl-1-azadienes,[11] their more easily handled 2-cyano derivatives,[12] and also by *N*-sulfonyl-1-azadienes.[13] In regards to the second type of 1-azadienes, the electron-donating substituent more commonly employed is the dialkylamino group. Thus dialkylhydrazones of α,β-unsubstituted aldehydes have been extensively used in the preparation of pyridines, quinolines, and mono-and diazaanthracenes (Figure 10).

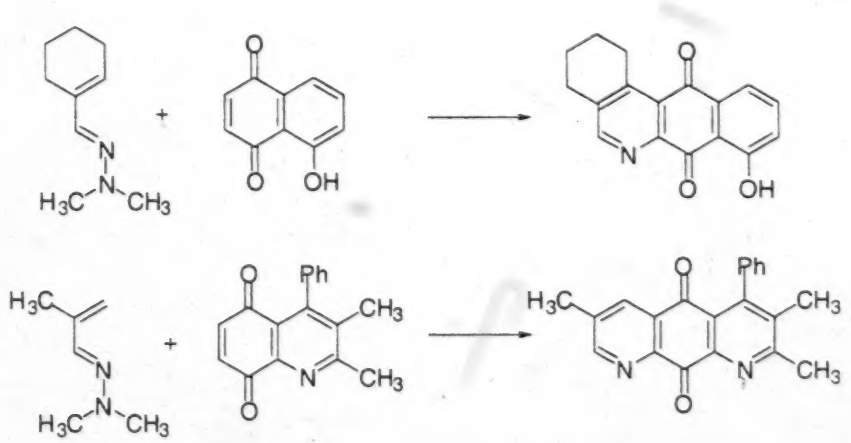
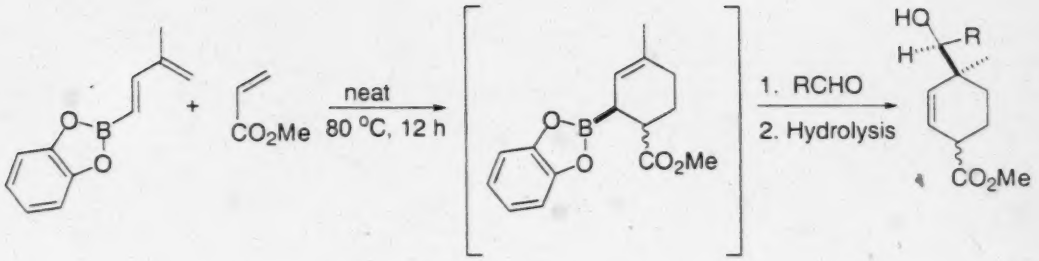


Figure 10. The use of dimethylhydrazones in the Diels-Alder reaction.

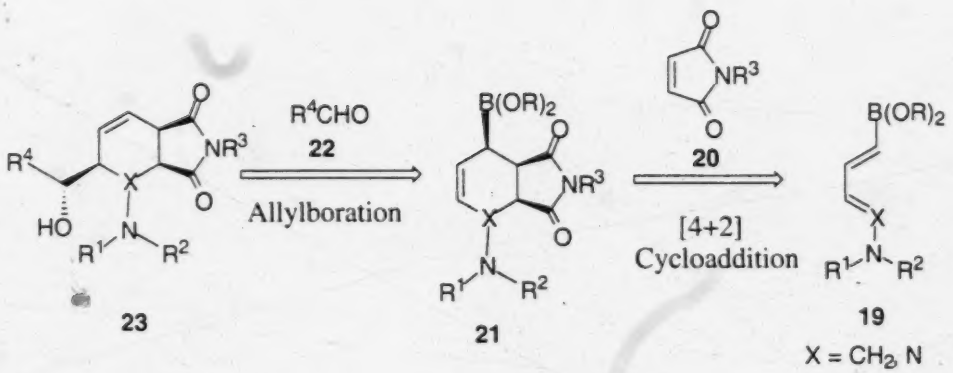
iv) The general approach.

Hetero[4+2] cycloadditions involving 1-dialkylamino-1,3-dienes and 1-borono-1,3-dienes have been reported.[14] However, the incorporation of both a dienylboronate moiety and a dialkylamine into the diene structure to give heterodiene of type **19** has not received any attention. The work of Vaultier and co-workers on the [4+2] cycloaddition of 1-boronobutadienes has shown the great versatility of these diene partners.[14] The use of the Diels-Alder reaction between dienophiles and 1,3-dienylboronates is a powerful method to obtain substituted cyclohexene derivatives containing an allylboronate moiety. The allylboronate offers a number of possibilities for further stereocontrolled functionalizations. Oxidation of the boronic acid moiety in the intermediate cycloadduct affords secondary alcohols while reaction of the allylboronate with aldehydes leads to secondary homoallylic alcohols with a very high level of diastereoselection. Recently, a stereoselective, one-pot tandem reaction investigated by Lallemand involves a Diels-Alder reaction of a 1,3-dienylboronate followed by the condensation with an aldehyde (Scheme 3).[15] On the basis of this report as a starting point, we proposed a retrosynthetic approach for the construction of polysubstituted α-hydroxyalkyl piperidine derivatives **23** (Scheme 4).

Scheme 3



Scheme 4



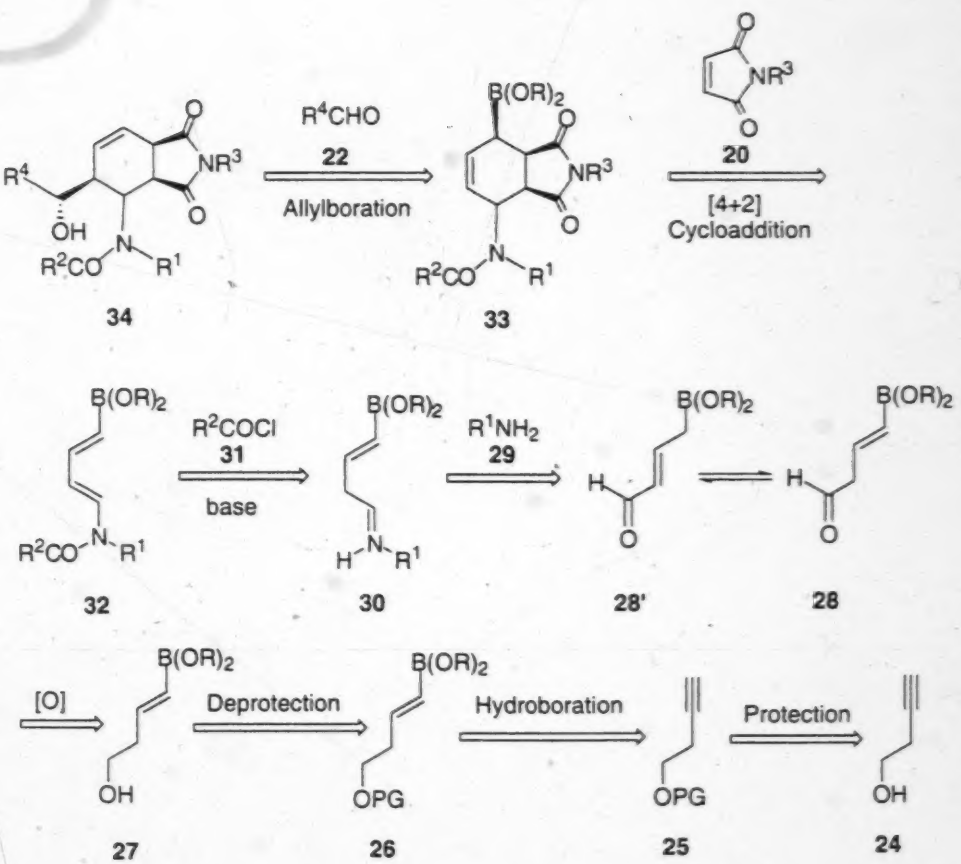
We propose to extend this powerful sequence to the use of 4-acylamino-1-borono-butadienes and other aza-heterodienes derived from aminoacids or amines. In Scheme 4, the diene's X group could be a methylene carbon or a nitrogen atom. The boronate intermediate will be obtained by using two different homologous aldehydes, as

shown in Schemes 5 and 6. For both strategies, the overall reactions are initiated by the [4+2] cycloaddition, followed by aldehyde allylboration to ultimately afford bicyclic β-amino alcohols **34** and **43**. In principle, as shown in Scheme 5, the selective *cis*-hydroboration of 3-butyn-1-ol should afford vinylboronic ester **27**. The resulting alcohol will be oxidized to aldehyde **28** by using the Swern methodology,[16] then converted to diene **32** by reacting with an amine (**29**) followed by an acid chloride (**31**), according to the method of Oppolzer.[17] The electron-donating effect of the 4-amino butadiene substituent should facilitate the cycloaddition with maleimides **20**. Aldehyde addition to **33** will trigger the allylboration reaction to give adduct **34**.

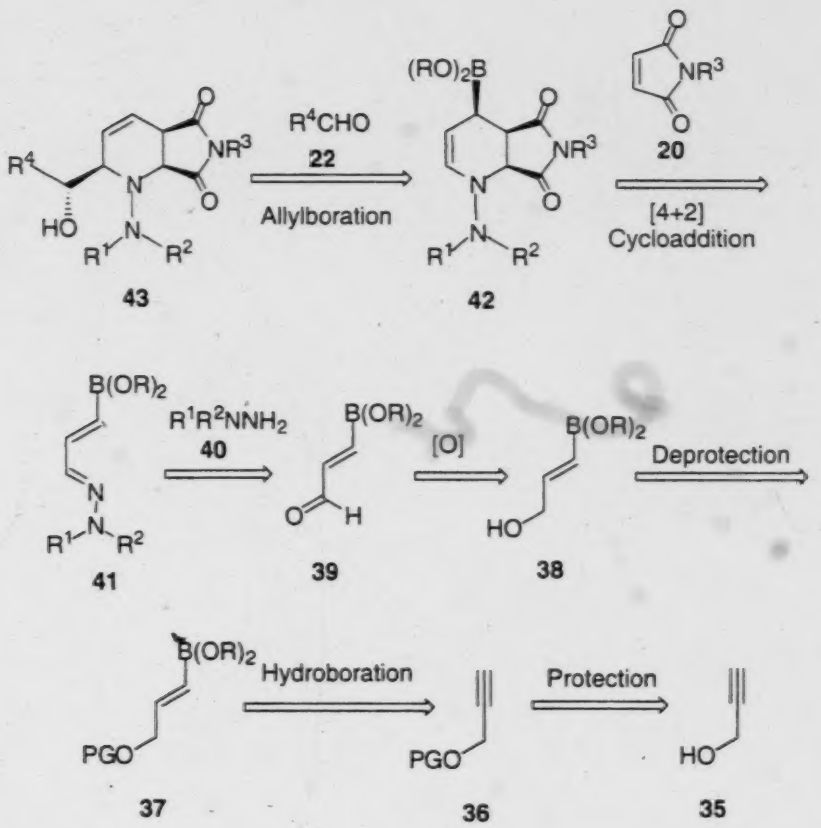
By using a hydrazine instead of an amine as illustrated in Scheme 6, one can change the product's functionality to give substituted piperidine derivatives **43**. In Scheme 6, the selective *cis*-hydroboration of propargyl alcohol followed by oxidation is expected to afford aldehyde **39**. The reaction with hydrazine **40** will afford azadiene **41**. The subsequent steps are similar to those described in Scheme 5. One advantage of this tandem, three-component [4+2] cycloaddition/allylboration sequence is the use of simple commercial reagents like *N*-substituted maleimides, aldehydes, amino acids, acid

chlorides and *N*,*N*-dialkylhydrazines. Also, compounds **34** and **43** can eventually be used as key intermediates in the synthesis of biologically active compounds like benzodiazepine mimetics (Schemes **23**, **24** and **25**, pages 65 and 66).

Scheme 5



Scheme 6


R4CHO
22
Allylboration
(RO)2B
NR3
20
[4+2]
Cycloaddition
43
42
B(OR)2
R1R2NNH2
40
41
39
[O]
38
Deprotection
Hydroboration
Protection
PGO
HO
37
36
35

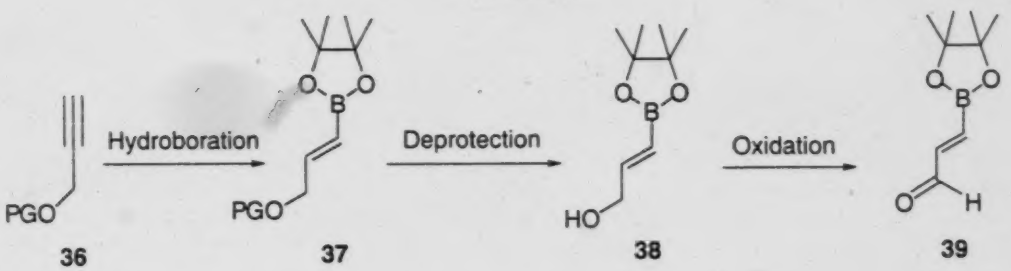
II. RESULTS AND DISCUSSION

A. Preparation and reactions of the dienes

i) Hydrazonodiene strategy.

We first explored the hydrazonodiene strategy (X = N as in Scheme 6). Two proposed routes were attempted to synthesize the key aldehyde intermediate **39** (Schemes 7 and 9). The first route involved the hydroboration of propargyl alcohol followed by boronate transesterification to a pinacol ester, deprotection and Swern oxidation of the primary alcohol (Scheme 7).

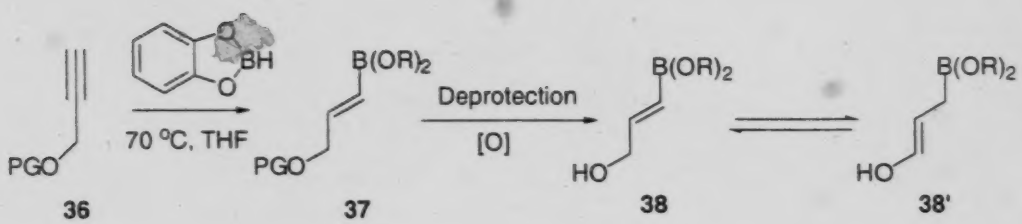
Scheme 7



Several different procedures were evaluated for the conversion of the alcohol **35** into the corresponding boronic ester **38**. Typically,

the first step involved the hydroboration of a protected propargyl alcohol derivative with catecholborane (CBH) at 70 °C (Scheme 8).[18]

Scheme 8

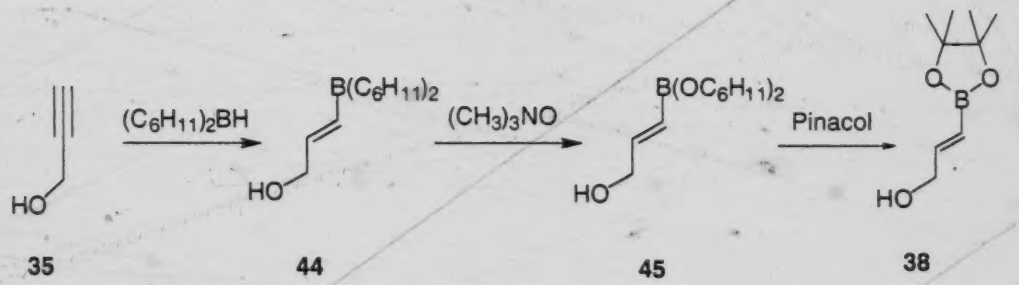


36 **37** **38** **38'**

However, application of these reaction conditions to alkyne **35** did not give rise to the desired product. Whereas CBH is a convenient boron hydride-reducing reagent, many unresolved problems were associated with its use. At least 1.5 equiv of CBH is usually required for hydroboration due to intrinsic side reactions such as alkene isomerization,[19] and BH_3 addition.[20] Another significant problem is the degradation of CBH under the reaction conditions.[21] Equally frustrating are the moisture, thermal and chromatography instability of the resulting catechol vinylboronates. Also, their direct preparation requires harsh reaction conditions (100 ^{0}C for alkenes and 130 ^{0} C for alkynes). Their transesterification to more stable boronic esters via the intermediate boronic acids is often necessary if further transformations have to be performed. In order to achieve the desired

transformation, we chose a three-step, one-pot procedure using the more reactive dicyclohexylborane (Scheme 9).[22] Selective oxidation of the sp^3 C-B bonds in **44** to B-O-C bonds in the resulting 1-alkenylborane **45** was possible with two equivalents of trimethylamine *N*-oxide dihydrate (TMAO). The reagent is exceptionally mild, permitting the oxidation of a wide variety of functionalised organoboranes. Subsequent transesterification with pinacol gave compound **38** in 65% yield (Scheme 9).

Scheme 9

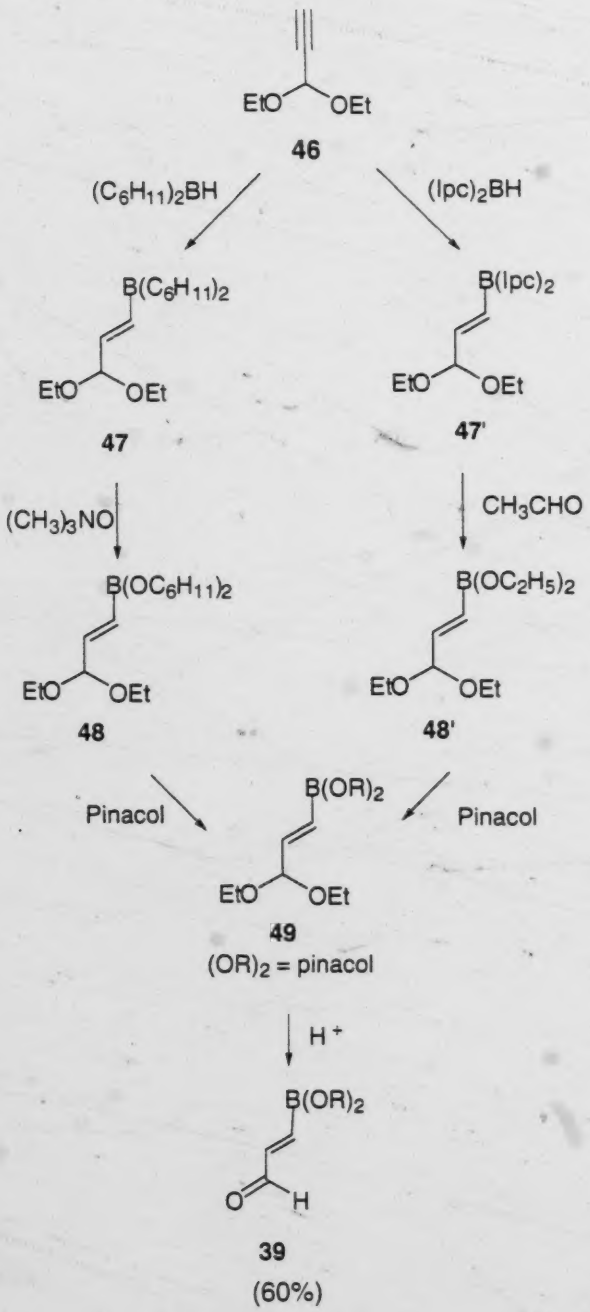


35 **44** **45** **38**

The next step was the Swern oxidation of the primary alcohol **38**. Unfortunately, the Swern oxidation of the alcohol never went to completion and it was difficult to separate the desired aldehyde product **39** from the reaction mixture. Several other oxidizing agents

were also investigated but gave unsatisfactory results. We then turned to the new route outlined in Scheme 10.[23] It involved acetal **46** as a starting material instead of alkynol **35**. Hydroboration of acetal **46** followed by oxidation and transesterification gave the corresponding boronate **49** (65% yield). Hydroboration can be carried out using either diisopinocampheylborane or dicyclohexylborane. Both led to the formation of product **39**. However, dicyclohexylborane gave better yields than diisopinocampheylborane and experimentally was easier to use. Thus, the aldehyde **39** was prepared according to the sequence depicted in Scheme 10 by using dicyclohexylborane. The addition of one equivalent of the acetal to a DME suspension of one equivalent of dicyclohexylborane at low temperature led to the *E*-vinylborane **47** exclusively. Two equivalents of TMAO were then added in small portions in such a manner that the solution is maintained under gentle reflux. This reaction led to the moisture sensitive boronate **48**, which was treated *in situ* with one equivalent of pinacol to give **49,** which was isolated in 65% yield by distillation. The acetal was removed by acid-catalyzed transacetalization using acetone, affording the required aldehyde **39** in pure form after distillation, in 60% yield.

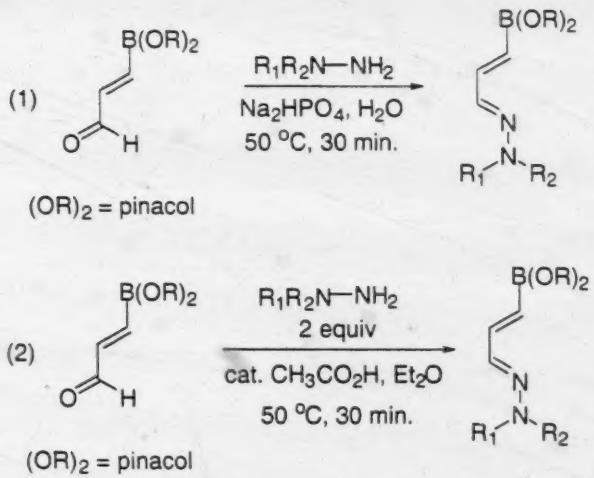
Scheme 10


EtO
OEt
46
$(C_6H_{11})_2BH$
$(Ipc)_2BH$
$B(C_6H_{11})_2$
$B(Ipc)_2$
47
47'
$(CH_3)_3NO$
CH_3CHO
$B(OC_6H_{11})_2$
$B(OC_2H_5)_2$
48
48'
Pinacol
Pinacol
$B(OR)_2$
49
$(OR)_2$ = pinacol
H^+
$B(OR)_2$
O
H
39
(60%)

The required hydrazonodienes **19** were obtained by the direct treatment of the corresponding hydrazine with the parent α,β-unsaturated compound **39** in a buffered aqueous solution (Method 1, Scheme 11)[24], or by condensation using a catalytic amount of acetic acid in diethyl ether (Method 2, Scheme 11)[25]. Both methods were found to be convenient and quite general, allowing the preparation of various dienes (Table 2, page 40). In general, dienes were obtained in very high yields with some minor amounts of the isomeric *Z*-vinylboronate. However, this isomer did not affect the efficiency of the tandem [4+2]/allylboration reaction. ^{1}H NMR of the recovered diene obtained from an incomplete tandem [4+2]/allylboration reaction shows no isomerization. Thus, the dienes were employed in the cycloaddition without further purification. These dienes were found to be quite stable to handling and could be conveniently stored for several weeks at low temperature (-20 °C).

Having established an efficient route to various 1-amino-1-aza-4-borono-1,3-butadienes, the stage was now set for probing their behaviour in the tandem [4+2]/allylboration reaction.

Scheme 11



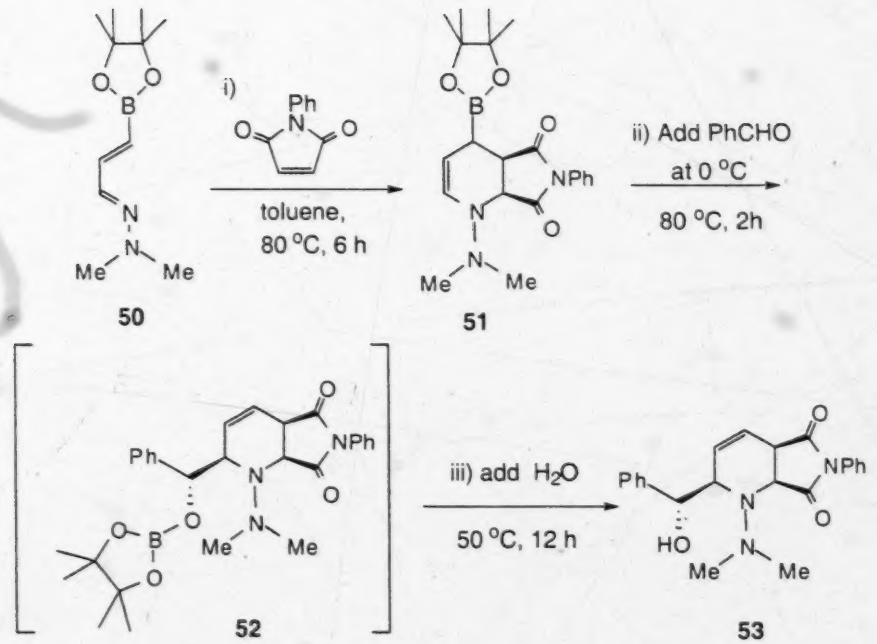
ii) Tandem [4+2]/allylboration reaction.

The bicycle **43** (Scheme 6) needed for our studies was unknown and required the development of a new synthetic methodology. For our investigation on novel heterodienes of type **41**, we chose to employ maleimides as model, electron-poor dienophiles since they are known to result in complete *endo*-selectivity in their reaction with 1-boronobutadienes. At this point, we considered two alternatives for the synthesis of bicyclic compound **43**. One possibility involved a two-step process: initial cycloaddition of the diene and the dienophile to form a cycloadduct **42** and then subsequent allylboration by adding

an aldehyde partner. Another possibility was to react all three components together in a one-pot reaction. This required that the aldehyde component used in the second step be inert to both the diene (**41**) and the maleimide partners, which react, together in the first step. We investigated the first possibility as a starting point. The initial Diels-Alder experiment was conducted using diene **50** obtained from *N*,*N*-dimethylhydrazine and *N*-phenylmaleimide at room temperature (Scheme 12). Under these conditions, the unstable cycloadduct could be observed by electrospray mass spectra but not by ^{1}H NMR. This reaction was found to proceed slowly at room temperature and longer reaction time (6 days) had no effect. Thus, the first step appeared not to be as straightforward as expected. This reaction could be run at reflux to effect the aza-Diels-Alder addition in shorter reaction times, but the desired adduct was accompanied by unidentified products. Realizing that Diels-Alder reactions are sensitive to thermal effects, we turned our attention to the tandem procedure. The allylboronate bicyclic intermediate **51** is not easy to isolate because of its sensitivity to air-oxidation. We therefore tried performing the cycloaddition in the presence of an aldehyde in order to trap the unstable intermediate allylboronate and obtain directly the corresponding alcohol products after hydrolysis. According to literature reports,[13] similar allylborations require high temperature (*i.e.* 80 °C). *N*-

Phenylmaleimide underwent cycloaddition at 80 °C and afforded the corresponding adduct **51** after 6 h, which was not isolated but converted directly to bicyclic product **53** after addition of benzaldehyde and hydrolysis (Scheme 12). A crude ^{1}H NMR spectrum showed minor amounts of the expected product. However, an electrospray mass spectra clearly showed the expected peak at *m/z* 378.2, corresponding to the molecular weight of the expected bicyclic product **53** $(M+H)^+$. The overall yield of the final product after purification was 25%. In addition to the obvious improvements needed to increase the yield in the [4+2]/allylboration reaction, the existing synthesis of the bicyclic product **53** needed to be optimized.

Scheme 12

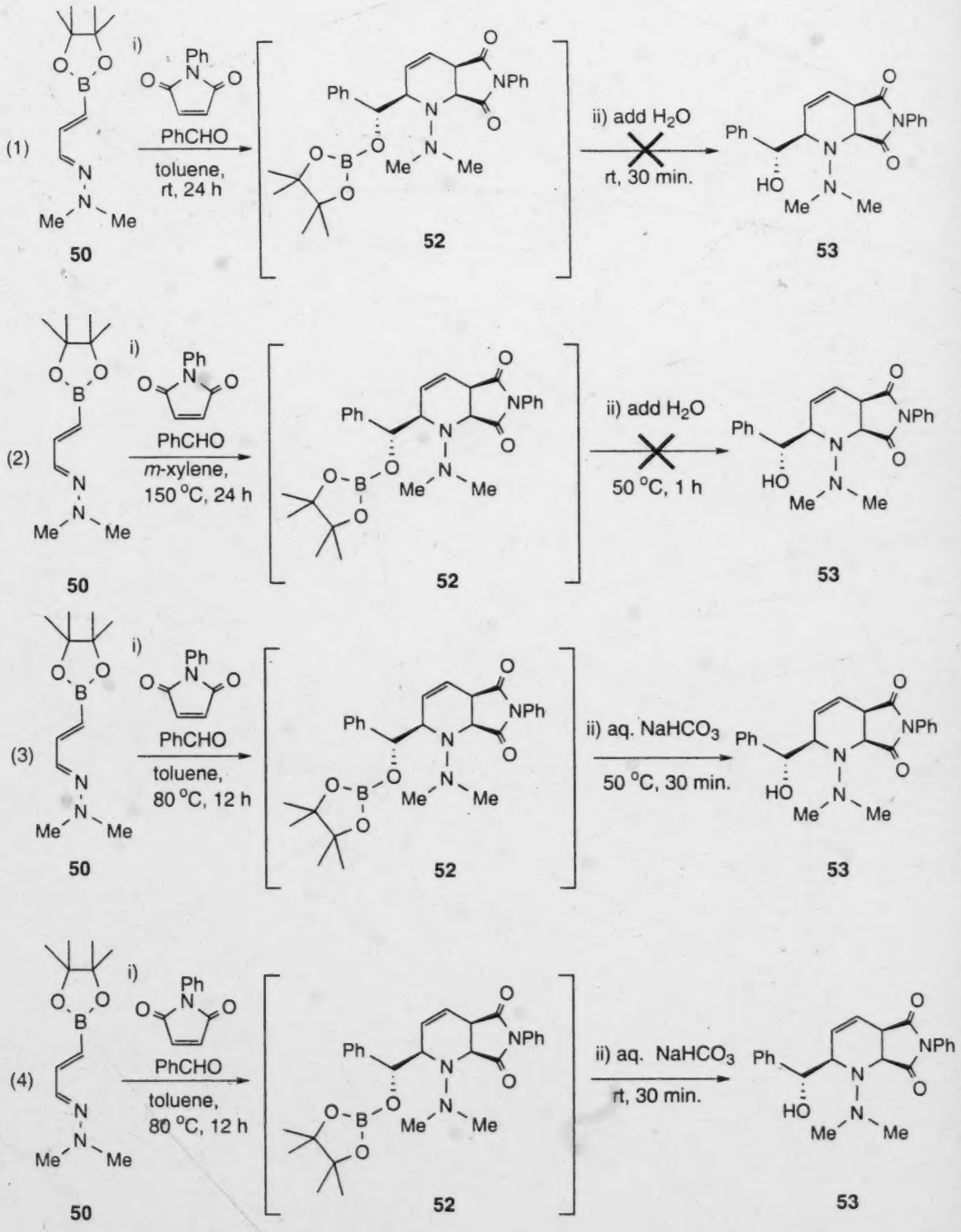


iii) Optimization of a one-pot tandem procedure.

Now that the feasibility of our tandem approach had been demonstrated, optimization of the [4+2]/allylboration could be undertaken. It was discovered that changing several features of the reaction was crucial for increasing the yield. The initial conditions tried for the synthesis of compound **53** are summarized in Scheme 13. Because the two-step process gave the expected product **53** in poor

yield from diene **50**, *N*-phenylmaleimide and benzaldehyde, we focused on the second possibility described in Scheme 13, a one-pot procedure. To this end, we employed equimolar amounts of the three model components. Very recently, a one-pot procedure for the [4+2]/allylboration reaction of boronobutadienes was reported by Lallemand and co-workers.[15] We evaluated the effect of solvent, temperature, work-up of the borate hydrolysis and extraction solvent. The first question to address was the proper choice of solvent. At this stage, we chose toluene since it allows higher reaction temperatures to be maintained. The temperature appeared to have a large effect on the [4+2]/allylboration reaction. Initially, temperatures between room temperature and 150 °C (in *m*-xylene) were studied. Mainly starting materials were recovered when the [4+2]/allylboration was performed at room temperature (Scheme 13, Equation 1). When the same reaction was carried out under more forcing conditions (above 120 °C), decomposition of **50** was observed (Scheme 13, Equation 2). Given that Vaultier's allylboration in the carbocyclic series requires moderate temperatures (*i.e.* 80 °C), we decided to carry out the one-pot [4+2]/allylboration reaction at 80 °C. The resulting borate **52** which formed upon allylboration needed to be hydrolysed to free the alcohol product. According to literature reports,[14] heating (*i.e.* 50 °C) in the presence of water is required for borate hydrolysis.

Scheme 13

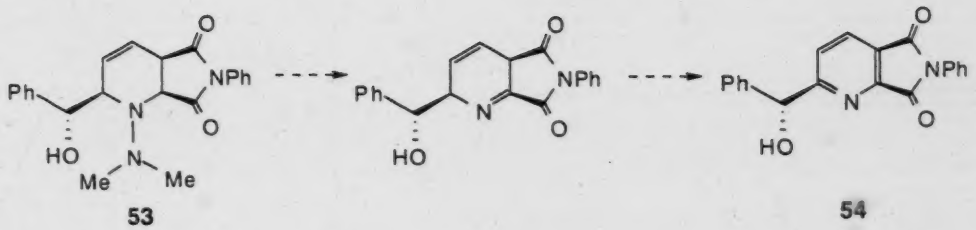

(1)
i)
PhCHO
toluene,
rt, 24 h
ii) add H_2O
rt, 30 min.
50
52
53
(2)
PhCHO
m-xylene,
150 °C, 24 h
ii) add H_2O
50 °C, 1 h
(3)
PhCHO
toluene,
80 °C, 12 h
ii) aq. $NaHCO_3$
50 °C, 30 min.
(4)
PhCHO
toluene,
80 °C, 12 h
ii) aq. $NaHCO_3$
rt, 30 min.

However, we discovered that stirring the final reaction mixture at 50 °C over a long period of time led to the decomposition of **52**. Fortunately, we found that conducting the neutral hydrolysis at room temperature instead of 50 °C could avoid decomposition. According to the one-pot procedure described by Lallemand and co-workers, a basic aqueous work-up can also be employed to hydrolyse the borate intermediate. However, it might lead to the formation of **54** by elimination of dimethylamine and subsequent aromatization by air-oxidation (Scheme 14, page 36). To our delight, a basic work-up with sodium hydrogen carbonate proceeded without any problems and provided clean hydrolysis of the borate intermediate. We tried the basic aqueous work-up at different temperatures, but the reaction provided higher yields at room temperature. The crude reaction mixture was purified by flash chromatography to afford the desired product **53** in 47% yield. Thus, in addition to the success of the one-pot procedure, the basic aqueous workup may allow further optimization of the process. It is noteworthy that the yields reported by Vaultier are no higher than 50%. Thus, the one-pot three-component reaction shown in Scheme 15 followed by a basic aqueous work-up appears most appropriate, and especially very practical towards solution-phase library synthesis compared to a two-step sequence. We also performed further studies to find out the optimal

amount of reagent and reaction times in order to further optimize this one-pot tandem process. To induce the complete cycloaddition of the model diene **50** with *N*-phenylmaleimide in an effective manner, it was necessary to use an excess of the dienophile (~2 equivalents). A survey of different reaction times was undertaken to determine the length of time for the tandem reaction (Table 1). Reaction times less than two days showed the presence of unreacted diene. Prolonging the reaction time to three days resulted in the complete consumption of diene **50** as observed by ^{1}H NMR of the crude reaction mixtures. Also, the extraction method greatly affected the yield of **53**. Solvents were screened in model studies to determine the most suitable extraction solvent for the [4+2]/allylboration reaction. With the given diene-dienophile-aldehyde system, ethyl acetate was found to be the best solvent for the extractive work-up (Table 1, entry 5), whereas **53** was obtained in poor yield when diethyl ether was used because of its low solubility in this solvent. We also tried the precipitation of **53** from ether, but the maleimide was obtained along with the product **53**. Thus, after completely surveying the reaction conditions for the [4+2]/allylboration, we found that the best reaction conditions were using one equivalent of diene, two equivalents of dienophile and one equivalent of aldehyde at 80 °C for 3 days (Table 1, entry 5). The resulting yield of 47% after flash chromatography under optimized

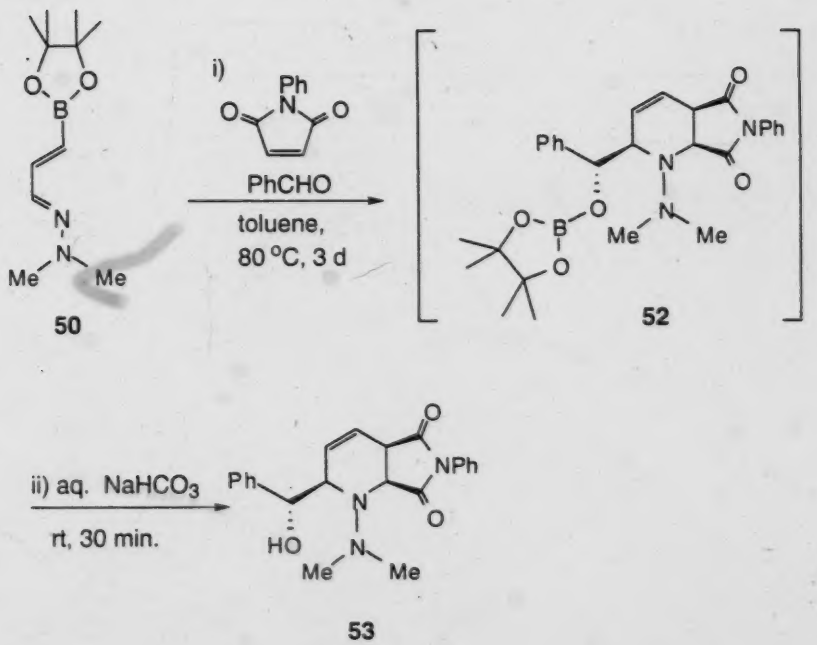
conditions is better than the one obtained in the two-pot reaction (25%).

Scheme 14



53 54

Scheme 15



50 52 53

Table 1. Allylboration reaction under different conditions.

Entry	Diene **50**	*N*-phenyl maleimide	PhCHO	T °C	Time (h)	Extraction Solvent	Crude yield (%)
1	1 equiv	1 equiv	1 equiv	80	16	EtOAc	a
2	1 equiv	1 equiv	1 equiv	80	24	EtOAc	a
3	1 equiv	2 equiv	1 equiv	80	16	EtOAc	a
4	1 equiv	2 equiv	1 equiv	80	24	EtOAc	a
5	1 equiv	2 equiv	1 equiv	80	3 days	EtOAc	80
6	1 equiv	3 equiv	1 equiv	80	12	EtOAc	a
7	1 equiv	3 equiv	1 equiv	80	24	EtOAc	a
8	1 equiv	3 equiv	1 equiv	80	3 days	EtOAc	78
9	1 equiv	2 equiv	1 equiv	80	3 days	CH_2Cl_2	70
10	1 equiv	2 equiv	1 equiv	80	3 days	Et_2O	40

a. Reaction was incomplete. ^{1}H NMR spectrum showed the presence of unreacted diene **50** in the approximate ratio of 1:4 with respect to the bicyclic product **53.**

iv) Substrate generality studies.

Our next objective was to test the generality of the one-pot tandem reaction. The standard optimized protocol described in Scheme 15 was applied to the synthesis of a series of different bicycles. The substituent variations that were employed are shown in Table 2. The reaction proved to be successful with a wide variety of

dienes, dienophiles and aldehydes. For example, entries 6-8 show a remarkable range of reactivity for azadienes obtained from monosubstituted phenylhydrazines, unsymmetrically substituted 1,1-dialkylhydrazines and acylhydrazines. We were worried that a phenylhydrazone might react by a 1,3-dipolar cycloaddition with *N*-phenylmaleimide, since the hydrazine can form a 1,3-dipolar tautomer by a proton shift from the terminal to the central nitrogen atom (Figure 11). Fortunately, we never observed this product; evidently, it reacts preferentially as an azadiene and gives **53f** as a single product. The maleimide functionality can also be changed (e.g. **53a** and **53b**). Furthermore, the isolation of bicycles **53c**, **53d** and **53e** show that electron-poor and electron-rich aromatic aldehydes, as well as saturated ones, could be employed as the aldehyde partner (Table 2, entries 3-5). Most importantly, the products were obtained as a single diastereoisomer, and with high homogeneity after flash chromatography purification. The level of purity determined by HPLC for **53a** and **53b** was 95% and >99% respectively. RP-HPLC analysis was performed on a Zorbax SB-C18 column (4.6 × 150 mm, 5 μm) using 40% acetonitrile/water mobile phases using UV detection at 230 and 210 nm, respectively. All products were fully characterized by ^{1}H NMR, ^{13}C NMR, MS and IR and obtained in 40-55% yields.

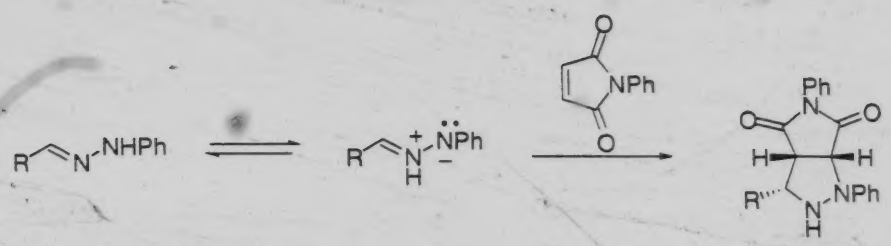


Figure 11. 1,3 dipolar cycloaddition of a phenyl hydrazone with *N*-phenylmaleimide.

Finally, an investigation of other dienophiles such as acrylates, fumarates and enol ethers was initiated to determine fully the scope and limitations of the tandem protocol. These dienophiles failed to give the expected bicyclic products under the standard reaction conditions. Enol ethers were tested toward inverse-electron demand cycloadditions, however these dienophiles also failed to provide the expected products. In addition, a pre-formed imine also failed as an allylboration substrate, in place of an aldehyde, to provide the expected product.

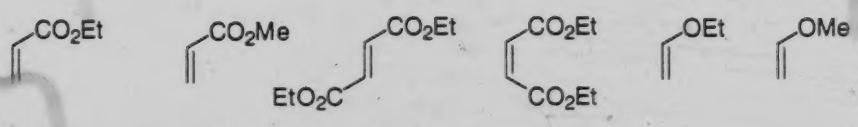
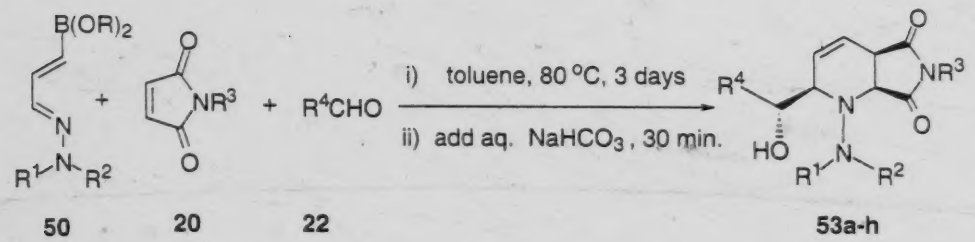


Figure 12. The use of other dienophiles in the tanden aza cycloaddition/allylboration reaction.

Table 2. Synthesis of bicyclic compounds 53a-h.



Entry	R^1	R^2	R^3	R^4	Bicyclic product	Yield[a] (%)
1	Me	Me	Ph	Ph	**53a**	47
2	Me	Me	Me	Ph	**53b**	50
3	Me	Me	Ph	4-NO_2-Ph	**53c**	48
4	Me	Me	Ph	4-MeO-Ph	**53d**	52
5	Me	Me	Ph	$CH_2CH(Me)_2$	**53e**	50
6	H	Ph	Ph	Ph	**53f**	46
7	Ph	Me	Ph	Ph	**53g**	46
8	H	Ac	Ph	Ph	**53h**	42

a. Isolated yields after flash-chromatography purification.

In our collaboration [with BioChem Pharma (Montréal)] efforts to apply these bicyclic compounds towards drug discovery, it is required that they should possess an adequate level of stability; that is, they should have a reasonable shelf life. To this end, we tested the stability of bicyclic products **53a** and **53g**. Three sets of different

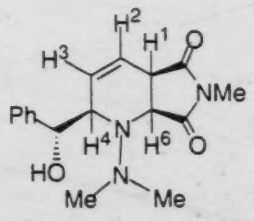
storage conditions were conducted. One sample was stored in a refrigerator, another was left on the benchtop in a sealed vial, and a third sample vial was left open on the benchtop. According to ^{1}H NMR analysis, all samples were found intact after a month, indicating that the hydrazonobicycles are relatively stable and could be stored for extended periods of time between different biological assays.

v) Optimization of yield.

The examples shown in Table 2 indicate the feasibility and generality of the tandem [4+2]/allylboration reaction. As shown in Table 1, two-fold excess of the dienophile is necessary to complete the reaction within 3 days. We carried out two sets of competitive experiments using an excess of both diene and dienophile. As shown in Table 2, two equivalents of *N*-methylmaleimide gave **53b** in 50% yield. However, three equivalents of the diene **50a** gave product **53b** in 80% yield with respect to *N*-methylmaleimide. This result indicates that reaction yields relative to the dienophile can be sufficiently improved by using an excess of diene. However, we decided to keep the diene as a limiting reagent for several reasons. The precursor **46** required to prepare the dienes **41** is expensive and its preparation rather tedious. It is also difficult to separate the expected

bicyclic product from the leftover diene. Also the use of the diene as limiting reagent (1 equiv) helps product purification towards high-throughput synthesis applications. Furthermore, a slight excess of dienophile is necessary to minimize the effects of diene degradation under the reaction conditions (3 days, 80 °C).

vi) NMR analysis of 53b.



The structures of bicyclic compounds **53a-53h** were supported by their spectroscopic data and mass spectral analysis. Unfortunately, some oily samples gave unsatisfactory combustion analyses results. ^{1}H NMR analysis of **53b** in $CDCl_3$ clearly showed two unsaturated protons H^3 and H^2 at 5.92 ppm (ddd, J = 1.6, 3.6, 10.6 Hz) and 5.66 ppm (ddd, J = 2.1, 4.4, 10.6 Hz), respectively. Distinguishing between these protons was accomplished by a COSY experiment. A COSY experiment was also used to assign the connectivity of the remaining protons in the 500 MHz ^{1}H NMR spectrum of **53b**. Protons H^{10} and H^6 appeared at 3.73 (d, J = 9.6 Hz) and 4.42 ppm (d, J = 8.5

Hz) respectively. Assignment of protons H^6 and H^{10} is further confirmed by protecting the hydroxy group using deuterated trichloroacetyl isocyanate (TAI) (Figure 13). TAI was used as an *in situ* derivatizing reagent for ^1H NMR studies of alcohols.[26] This reagent is very effective as it reacts almost instantaneously with primary or secondary hydroxyl groups, produces no ^1H NMR peaks of its own and has a good shelf life. It produces a downfield shift of about 0.5 to 0.9 ppm for hydrogen atoms geminal to primary hydroxyl groups compared with shifts of about 1.0 to 1.6 ppm for hydrogen atoms geminal to secondary hydroxyl groups. Figure 13 shows the ^1H NMR of **53b** before and after addition of TAI. The proton H^{10} at 3.73 ppm has shifted to 5.38 ppm. The observed shift of 1.65 ppm suggests that the proton H^{10} is geminal to a secondary hydroxyl group. The sharp peaks at 3.05 ppm and 2.46 ppm represent the NCH_3 and $N(CH_3)_2$ groups, respectively. Alllylic protons H^1 and H^4 appeared between 3.40-3.45 ppm as overlapping signals. The hydroxyl proton was displayed at 4.26 ppm as a broad peak. The peak at 1.60 ppm is a water peak from $CDCl_3$ solvent. The ^{13}C NMR (APT) spectrum displayed two signals for carbonyl groups, one signal for the quaternary carbon in the aromatic ring, nine signals for methines CH groups and two signals for CH_3 groups. In the low-resolution electrospray mass spectrum, the major peak at *m/z* 338 corresponds to

$(M+Na)^+$, the peak at *m/z* 316 corresponds to $(M+H)^+$ and the peak at *m/z* 298 corresponds to $(M+H-H_2O)^+$. In the high-resolution mass spectrum, the molecular peak at 338.1480 confirms its composition as $C_{17}H_{21}N_3O_3Na$. In its infrared spectrum, a sharp carbonyl band appears at 1705 cm^{-1} and a broad hydroxyl band at 3500 cm^{-1}.

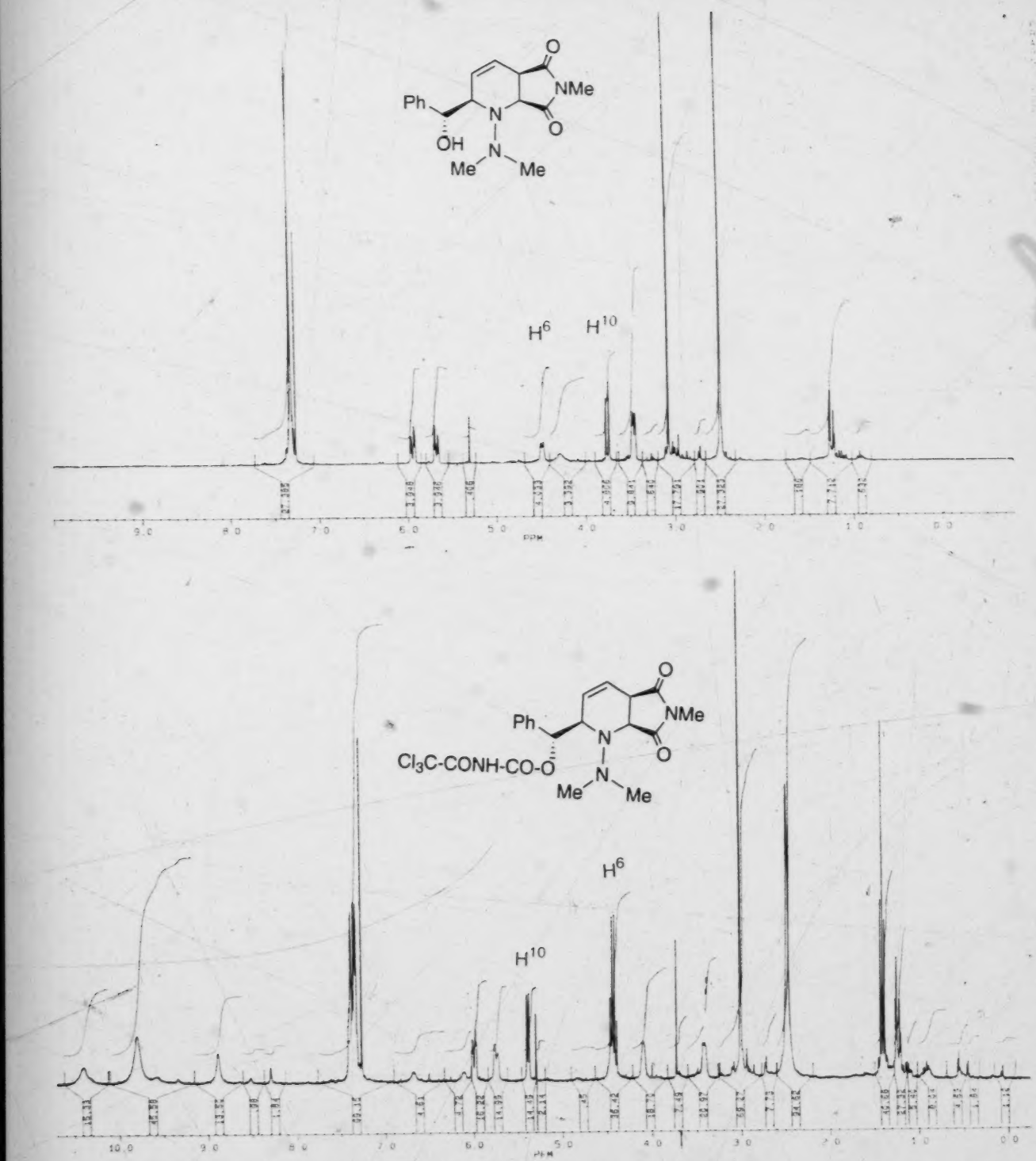


Figure 13. ^{1}H NMR spectra of **53b** and its trichloroacetyl isocyanate derivative.

vii) Structure determination of 53b.

It was found impossible to confirm the stereochemistry of the bicyclic products using NOE experiments. Thus, the X-ray crystal structure analysis of a bicyclic product was necessary to assign the relative stereochemistry from the allylboration step. There are two new stereogenic centers formed in the allylboration step, leading to four possible stereoisomers of the β-amino alcohol products (Figure 14). The hydroxyalkyl side chain could be *syn* or *anti* to the maleimide unit.

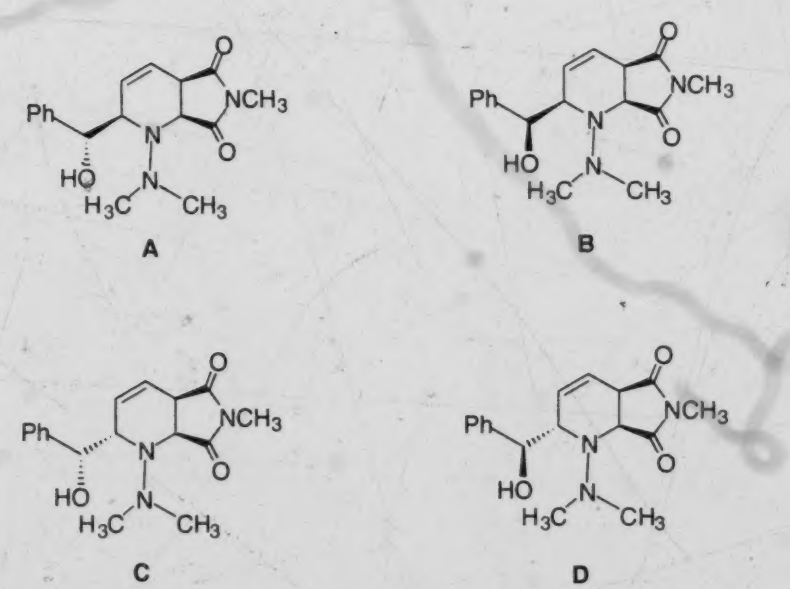
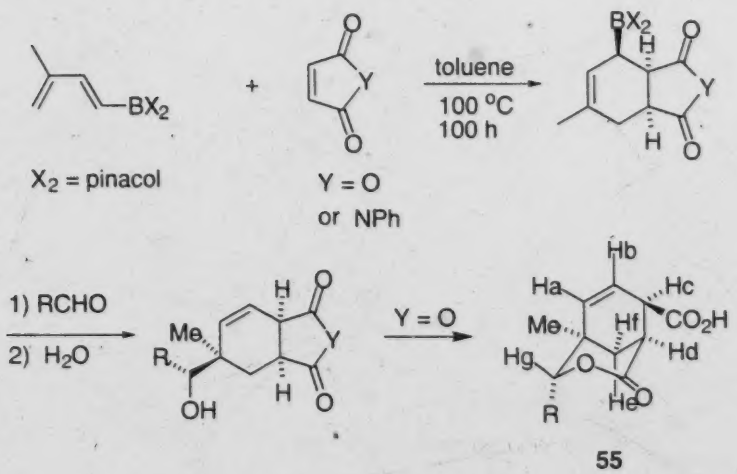


Figure 14. All possible β-amino alcohol diastereomers of **53b**.

According to the work done by Vaultier and others on the carbocyclic series,[14] the expected stereochemistry is the one where the hydroxyalkyl side chain and the maleimide unit are cis to each other. In his work, the configuration of the newly formed stereogenic centers was established on the basis of the ^1H NMR data of the bicyclic lactones **55** formed via intramolecular alcoholysis of the anhydride cycloadduct.

Scheme 16



We envisioned that an open transition state could compete where the hydrazine nitrogen coordinates to the boronic ester (Figure 15), thereby preventing attack of the aldehyde from the top face. An attack of an aldehyde from the bottom face would result in

stereoisomers **C** or **D**. However, this possibility seemed unlikely. To the best of our knowledge, there are no examples of allylboration reactions proceeding via an open transition state.

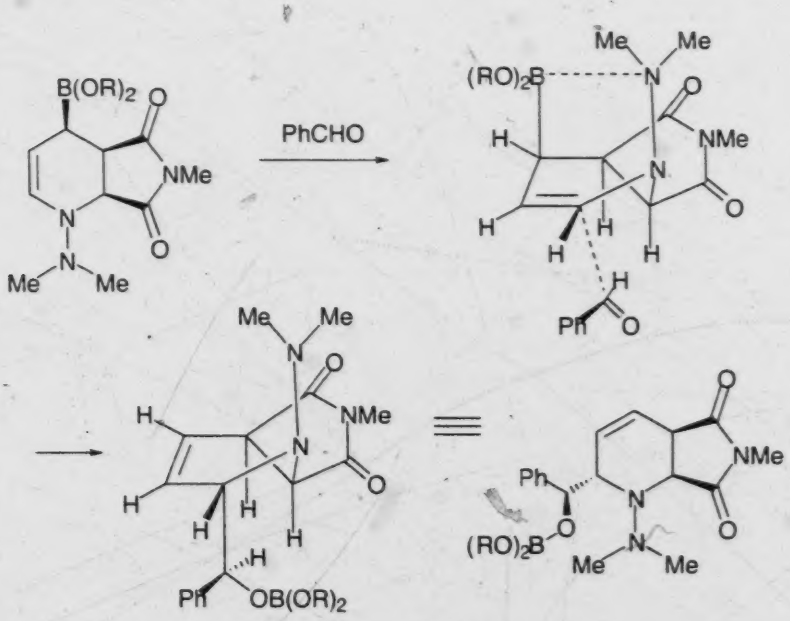
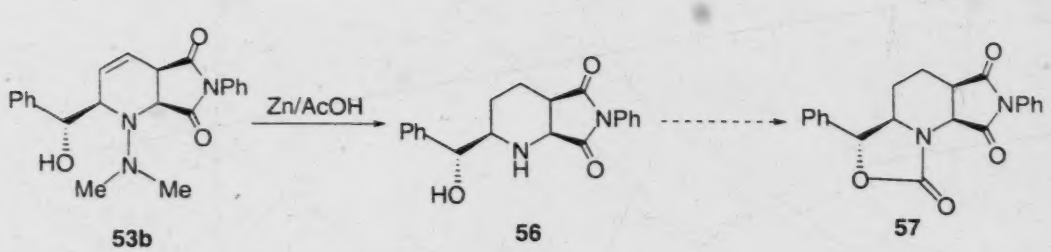


Figure 15. Possible open transition state leading to **53b**.

Compounds **53a** and **53b** were easy to crystallize. However, the crystals did not diffract properly. Several unsuccessful attempts were made to obtain suitable crystals of **53a** and **53b**. Finally, we decided to make the rigid, saturated tricyclic compound **57**, which would preserve the relative stereochemistry arising from the allylboration step (Scheme 17).

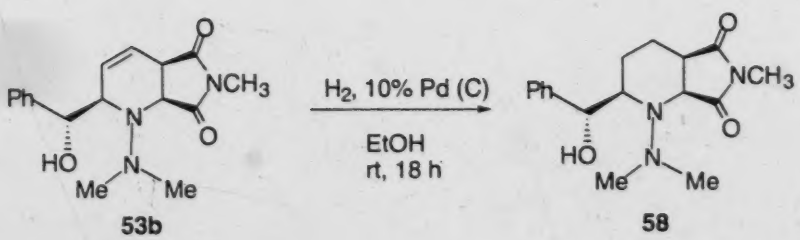
Scheme 17



This transformation can be achieved by cleaving the N-N hydrazine bond and reacting the aminoalcohol product with triphosgene to form the carbamate derivative **57**. According to literature reports, the hydrazine bond can be easily cleaved either by using zinc in acetic acid[27] or by hydrogenolysis.[28] By using the first method, two products were obtained. The major one showed complete reduction of the double bond along with cleavage of the N-N bond, and the minor one with the double bond remaining intact. However, we decided to carry out our study with the completely reduced product. In order to obtain the fully saturated product **56**, a prolonged reaction time was required. However, ^{1}H NMR revealed that this procedure led to epimerisation at the C10 position. Also, the zinc promoted reduction followed by carbamate formation led to the expected product only in poor yields. Therefore, this approach was abandoned. We then turned to the hydrogenolysis using Pd(C) at room temperature overnight. However,

this method failed to give the expected product **56**. To confirm the relative stereochemistry of the hydrazonobicycles, the initial adduct **53b** was subjected to reduction with Pd(C) and hydrogen, which gave the corresponding bicycle **58** with complete reduction of the double bond (Scheme 18). Slow evaporation of a solution of **58** in dichloromethane gave suitable crystals that led to a successful diffraction analysis and the X-ray generated structure by R. McDonald shown in Figure 16. This revealed that we obtained the same stereochemistry for the β-amino alcohol unit as in the carbocyclic series of Vaultier.[8]

Scheme 18



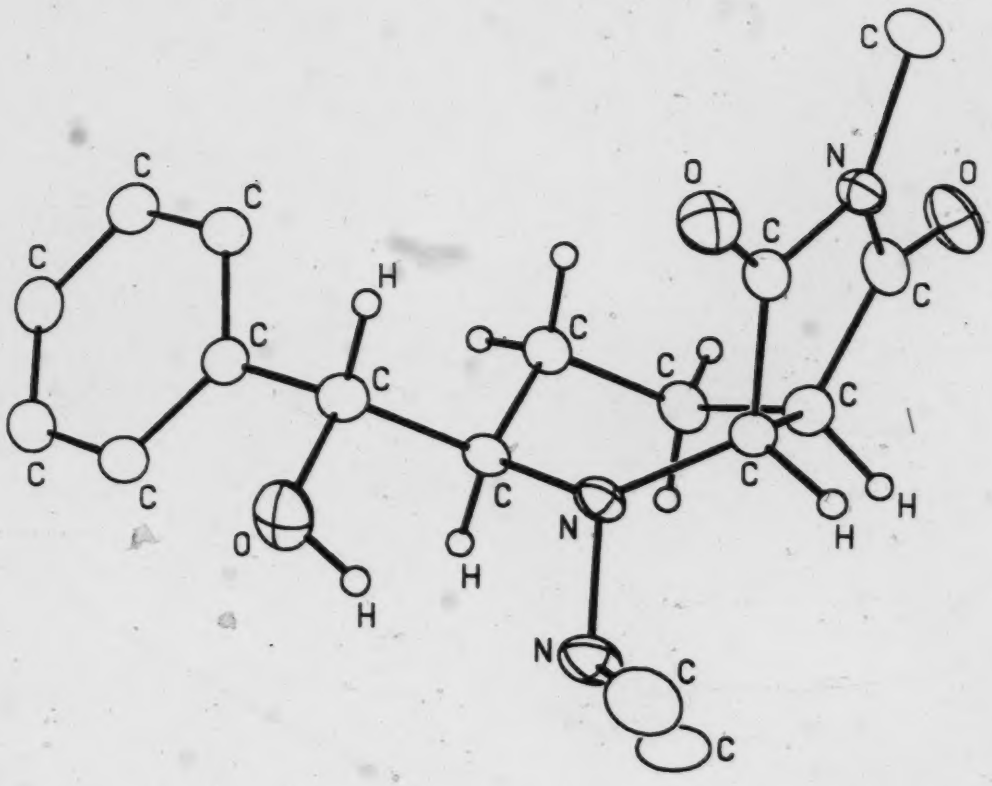


Figure 16. X-ray crystal structure of **58**.

At first it was reasonable to assume that the [4+2] cycloaddition step proceeded to give the *endo* adduct. From the latter, the stereochemical outcome of the allylboration step could be explained via a cyclic chair-like transition state involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the piperidine ring (Figure 17).

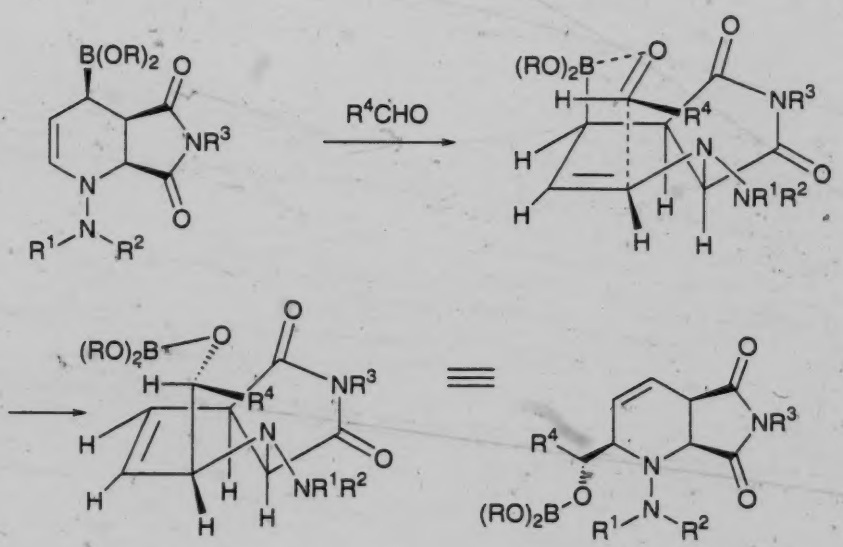


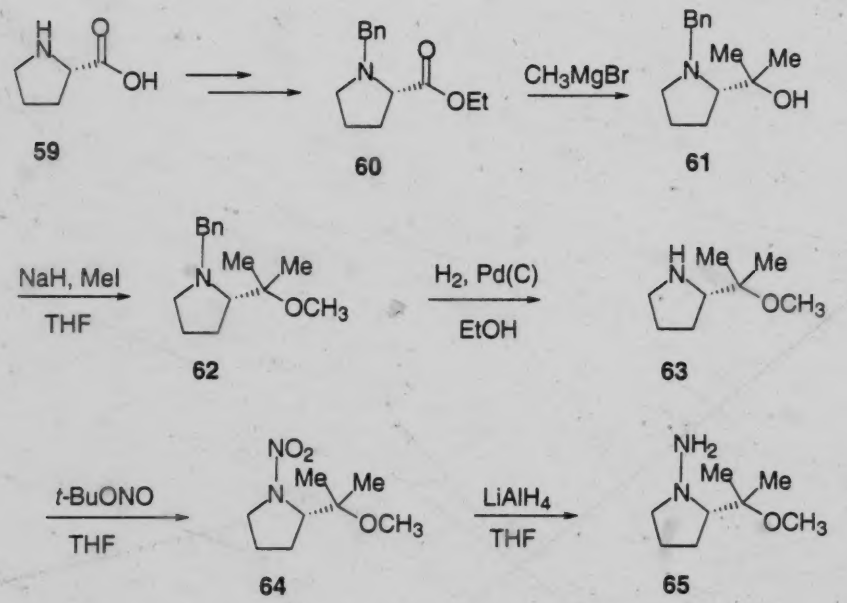
Figure 17. Proposed transition state leading to **53b**.

viii) Route to enantiopure bicycles.

The stereodifferentiating characteristics of the tandem [4+2]/allylboration could be profitably enhanced if this reaction is performed on a chiral diene precursor. According to literature reports,[29] SAMP [(S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine]- or RAMP [(R)-(+)-1-amino-2-(methoxymethyl)pyrrolidine]-derived dienes lacking the boronic ester substituent readily undergo [4+2] cycloaddition to give adducts with d.e.'s as high as 98%. On the basis of such a strategy, we extended our method to the preparation of enantiomerically pure bicycles by using proline-derived hydrazones **66a** and **66b** (Scheme 20). SAMP is commercially available, whereas SADP (**65**) [(S)-(-)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine] is prepared using a literature procedure.[30] As described in Scheme 19, (S)-proline was esterified to the ethyl ester via the acid chloride and after addition of trimethylamine, the resulting crude (S)-proline ethyl ester was treated with crude benzyl-*N*,*N*-dicyclohexyl-isourea, prepared in quantitative yield from dicyclohexylcarbodiimide and benzylalcohol under cuprous chloride catalysis. This procedure gave **60** in 40% yield based on (S)-proline. Addition of methylmagnesium bromide to the benzyl protected proline ester **60** afforded the *N*-benzylated tertiary alcohol **61** as the key intermediate in the reaction

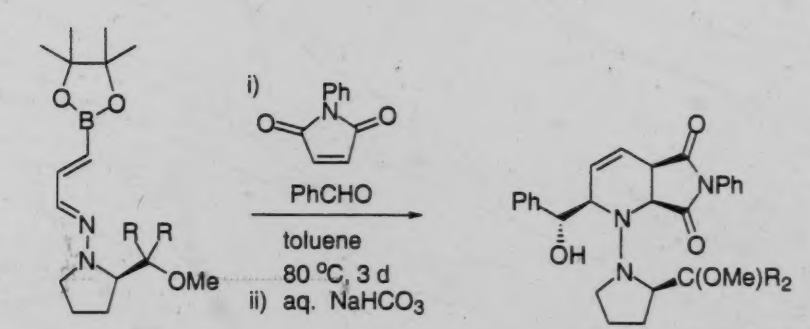
sequence. The alcohol group was readily converted to the methyl ether **62** by treatment with sodium hydride and methyl iodide in tetrahydrofuran. Deprotection by hydrogenolysis gave rise to the aminoether **63**, which could easily be converted further to the corresponding hydrazine **65** by nitrosation with *t*-BuONO in THF followed by reduction with $LiAlH_4$.

Scheme 19



SAMP derived hydrazones derived from α,β-unsaturated aldehyde **39** reacted as electron-rich dienes with *N*-phenylmaleimide (Scheme 20). The subsequent allylboration with benzaldehyde gave bicycles **67a** and **67b** with diastereomeric excesses of 80% and >95% respectively, as determined by ^{1}H NMR analysis of the crude reaction mixtures. Attempts to purify the minor isomer have not yet been successful. These bicyclic products could be converted into substituted piperidines by cleavage of the N-N bond. The absolute stereochemistry is unknown at this stage. However, we are attempting to obtain suitable crystals of **67b** in order to define its absolute and relative stereochemistry by X-ray diffraction analysis.

Scheme 20



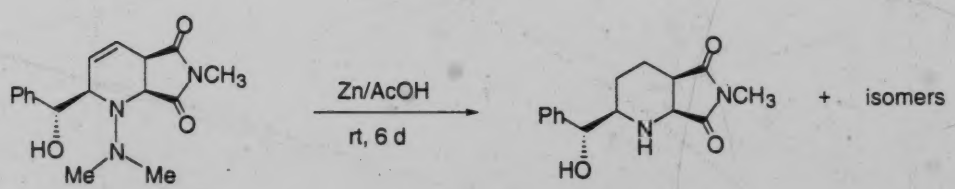
66 a = R = H
66 b = R = CH_3

67 a = R = H: 80% d.e
67 b = R = Me: >95% d.e

ix) Reductive cleavage of the hydrazine.

The synthetic usefulness of the tandem [4+2]/allylboration would rest upon the possibility of removing the often undesired dimethylamine substituent in the adducts. According to literature reports,[27] this operation can be readily effected with zinc in acetic acid. We carried out the reaction of **53b** with three equivalents of zinc in acetic acid for 1 hr at 80 ^{0}C. The mixture was then brought to pH 8 with a 10% aqueous solution of sodium carbonate. Extraction with methylene chloride and purification by flash chromatography led to an apparent mixture of epimers at C10 and rather poor overall yields. Instead of 80 ^{0}C, we tried the same reaction at room temperature for a prolonged period (6 days) to improve the yield (Scheme 21). However, we were not successful in optimizing the yield to more than 20%. At last, we abandoned this method and turned to a new one.

Scheme 21

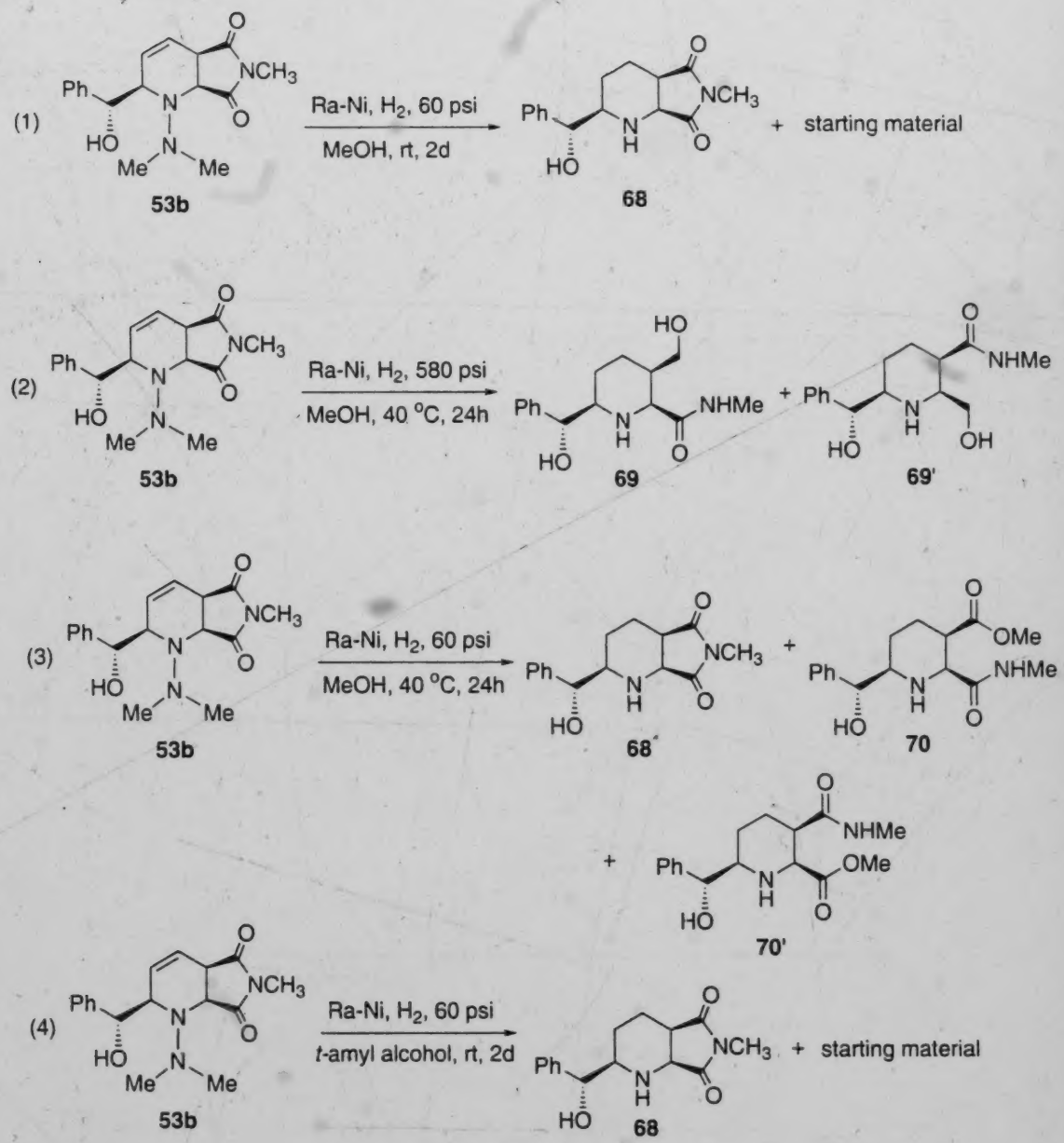


53b **68**

The second method, which gave a better result involved the use of

Raney nickel under hydrogen pressure in methanol (Scheme 22). The ^{1}H NMR spectrum looks much cleaner and purification is easier compared to the first method. In an effort to develop a better understanding of the process involved in the hydrazine cleavage, two sets of experiments at different temperatures and pressures were conducted. As shown in Scheme 22, low-pressure hydrogenolysis gave a mixture of the desired product **68** with reduced double bond, along with some traces of starting material (Scheme 22, Equation 1). On the other hand, higher pressure and temperature gave a mixture of **69** and **69'** (Scheme 22, Equation 2). This outcome can be explained by the opening of the imide ring by methanol and subsequent reduction to give two regioisomeric alcohols. Reaction at low pressure and moderate temperature (*i.e.* 40 °C) gave the expected product **68** in 50% along with two regioisomeric esters **70** and **70'** (Scheme 22, Equation 3). We decided to optimize the reductive cleavage by carrying out the reaction at low pressure for a longer period of time and using non-alcoholic or hindered tertiary alcohol solvents like *t*-amyl alcohol (Scheme 22, Equation 4). However, we obtained a mixture of the desired product **68**, along with some traces of starting material. At this point, we have not been successful in obtaining the expected product **68** as the only product. We are still working on this strategy.

Scheme 22


(1)
Ra-Ni, H2, 60 psi
MeOH, rt, 2d
+ starting material
53b
68
(2)
Ra-Ni, H2, 580 psi
MeOH, 40 °C, 24h
53b
69
69'
(3)
Ra-Ni, H2, 60 psi
MeOH, 40 °C, 24h
53b
68
70
70'
(4)
Ra-Ni, H2, 60 psi
t-amyl alcohol, rt, 2d
+ starting material
53b
68

x) Work towards a high-throughput purification protocol.

As described earlier, two equivalents of the dienophile are required to complete the one-pot reaction. ^{1}H NMR analysis of crude **53a** showed the presence of unreacted dienophile as well as free pinacolborate. In order to apply our multicomponent reaction to combinatorial chemistry, we have explored ways to simplify the purification procedure to avoid a lengthy chromatography step. The use of insoluble supports facilitates high throughput synthesis by simplifying compound purification to simple resin filtration and washing. The use of scavenger resins to eliminate excess reagents is also a promising strategy in the solution phase synthesis of parallel libraries. In the first place, we used a thiol-polystyrene (PS) resin to eliminate excess maleimide. Crude **53a** (1 equiv) was added to a polypropylene filter vessel containing a suspension of thiol-PS resin (1 equiv) in dry THF. The vessel was shaken for an hour after which the resin was rinsed with dry THF several times. It was found that this method works well using three equivalents of thiol-PS resin. The next task was the removal of the pinacolborate ester, the by-product of the allylboration step. To this end, we tried DEAM-PS (*N*,*N*-diethanolaminomethyl polystyrene) resin prepared in our laboratory (Chapter 2, Scheme 2.1).[2] DEAM-PS resin can immobilize aryl,

alkenyl, and alkyl boronic acids quantitatively in a wide range of organic solvents. In this regard, DEAM-PS resin could be very useful to scavenge released boronic acids. However, this resin did not effectively immobilize the pinacolborate ester. We also tried a C18 reverse-extraction cartridge in order to obtain the pure product **53a**. A solution of crude **53a** in methanol was filtered through the cartridge. The column was rinsed with 5.0 mL portions of different solvent systems *i. e.* MeOH, MeOH/THF, THF, EtOAc, Et_2O, Et_2O/hexane and hexane. We found that **53a** elutes with MeOH along with *N*-phenylmaleimide. We tried to use a 25% H_2O/MeOH system, but the same result was obtained. We also filtered crude **53a** through a short plug of silica gel rinsing it several times with toluene. ^1H NMR of **53a** showed only traces of pinacolborate ester and free pinacol. This indicated that we could remove the residual pinacol and other polar impurities by rinsing the column several times with toluene to elute the bicyclic product **53a**.

B. Plans toward solid-phase synthesis.

There is an enormous interest in the development of solid-phase synthetic approaches to small molecules, particularly those that contain polyfunctional heterocycles. As part of our laboratory's

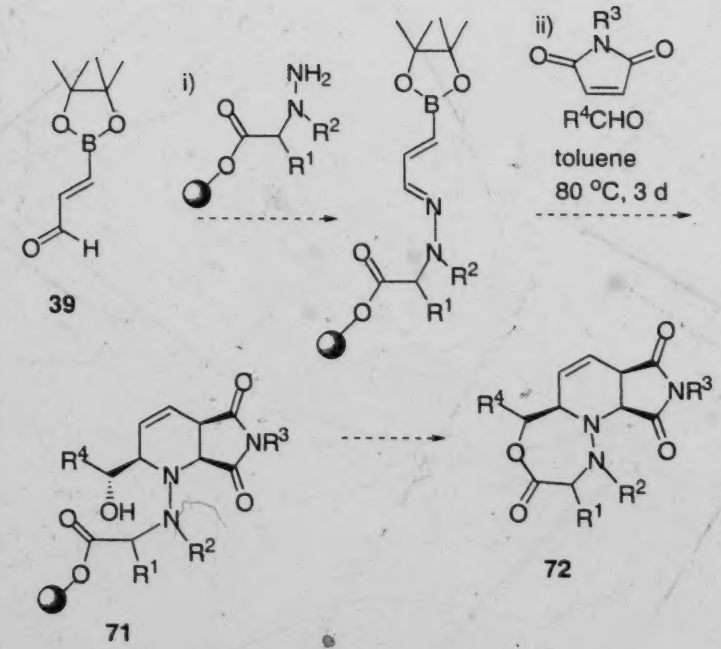
programme in solid-phase synthetic methods, we have an interest in developing strategies and methodologies applicable to a combinatorial approach to nitrogen-containing heterocycles.

Thus, as a result of our successful efforts with the hydrazonodiene approach in solution phase, we were encouraged to apply this strategy on solid-phase. Herein, we describe preliminary efforts towards the construction of benzodiazepine-like derivatives in which four substituents could be independently varied on the solid support. At first, we performed a control experiment where the stability of bicycle **53a** in 50% trifluoroacetic acid /CH_2Cl_2 for 2 hours was confirmed. Thus, TFA cleavable resin linkers could possibly be employed toward solid-phase applications. Several linking strategies have been proposed to allow the incorporation of four independent R groups using the tandem [4+2]/allylboration chemistry. As shown in Scheme 23, the condensation of an α-amino ester with aldehyde **39**, followed by the tandem [4+2]/allylboration would afford product **71**. Finally, the resin could be cleaved and the corresponding alcohol cyclized concomitantly to form a seven-membered lactone **72**. As shown in Scheme 24, we could also acylate the secondary amine of a monosubstituted hydrazine chain. Coupling of the secondary amine with various Fmoc protected amino acids followed by mesylation of

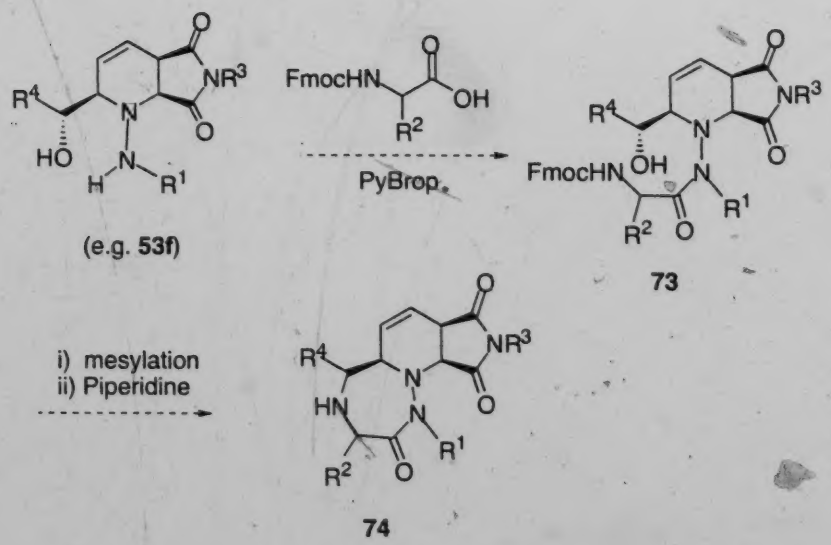
the secondary alcohol and cleavage of the Fmoc group with piperidine would promote subsequent cyclization to afford the 1,4-diazepine-2-one derivative **74**. As shown in Scheme 25, a similar bicycle could be coupled to an *o*-nitro–phenylsulfonyl-protected amino acid, followed by a Mitsunobu reaction and sulfonamide cleavage. As shown in Scheme 26, we could link the bicyclic structure to a solid support via the maleimide substituent. We decided to follow this strategy as a first approach to solid-phase applications. We first attempted to construct the required maleimide on solid support (Schemes 27, Equations 1 and 2). As shown in Equation 1, the trityl chloride derivative **78** is converted to the intermediate maleimic acid **79**, which is then cyclized under acidic conditions to give maleimide anhydride on trityl derived support **80**.[31] However, only a small amount of impure material was released after cleavage of resin **80**. We then turned to the Mitsunobu approach shown in Equation 2. It is potentially more general since it can be carried out under essentially neutral conditions and at room temperature. However, this approach was not very successful either (Scheme 27, Equation 2). Finally, we decided to prepare a bifunctional molecule that contains a free amino or alcohol group and a maleimide group in solution (Scheme 27, Equation 3).[32] The free amine or alcohol would then be coupled to trityl chloride resin. This procedure based on a pre-formed maleimide

will minimize the number of operations on solid support. Moreover, the coupling reaction of an alcohol or a secondary amine onto trityl chloride resin is straightforward. We considered constructing the required maleimide derivatives with 3-aminopropanol via the two-step condensation of maleic anhydride. This approach was not very successful in solution because of assisted maleimide ring opening. We then tried a Mitsunobu approach where we tried 2-aminopropanol instead of 3-aminopropanol. We are still working on this approach. Our laboratory will keep working on optimizing this chemistry and pursuing applications of the tandem [4+2]/allylboration reactions to solid-phase library synthesis.

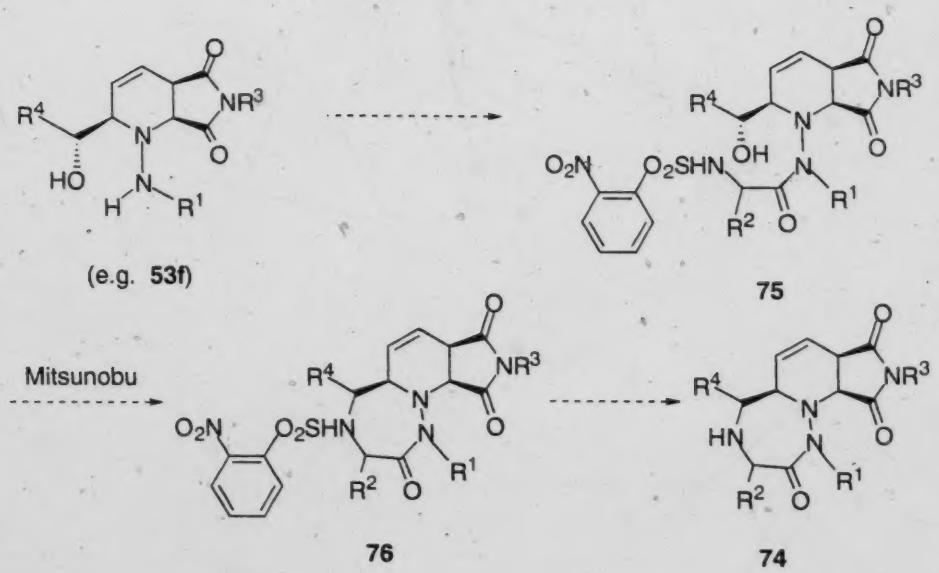
Scheme 23



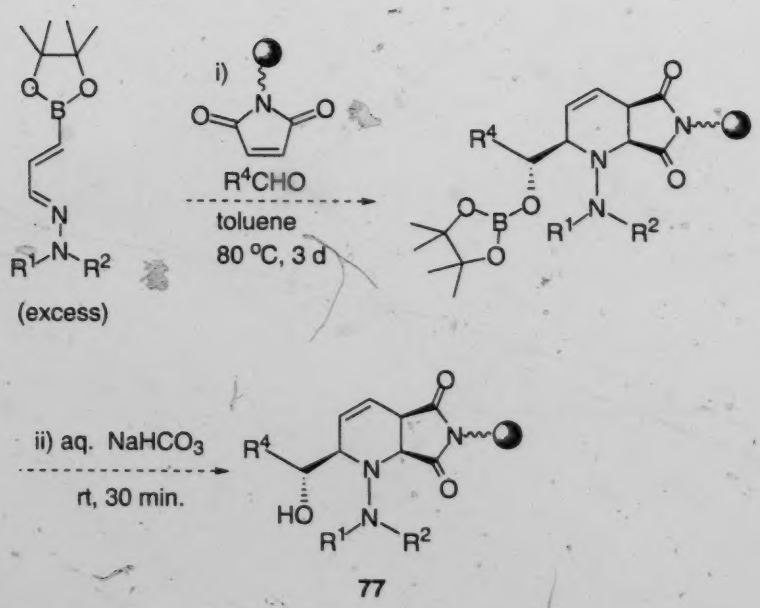
Scheme 24



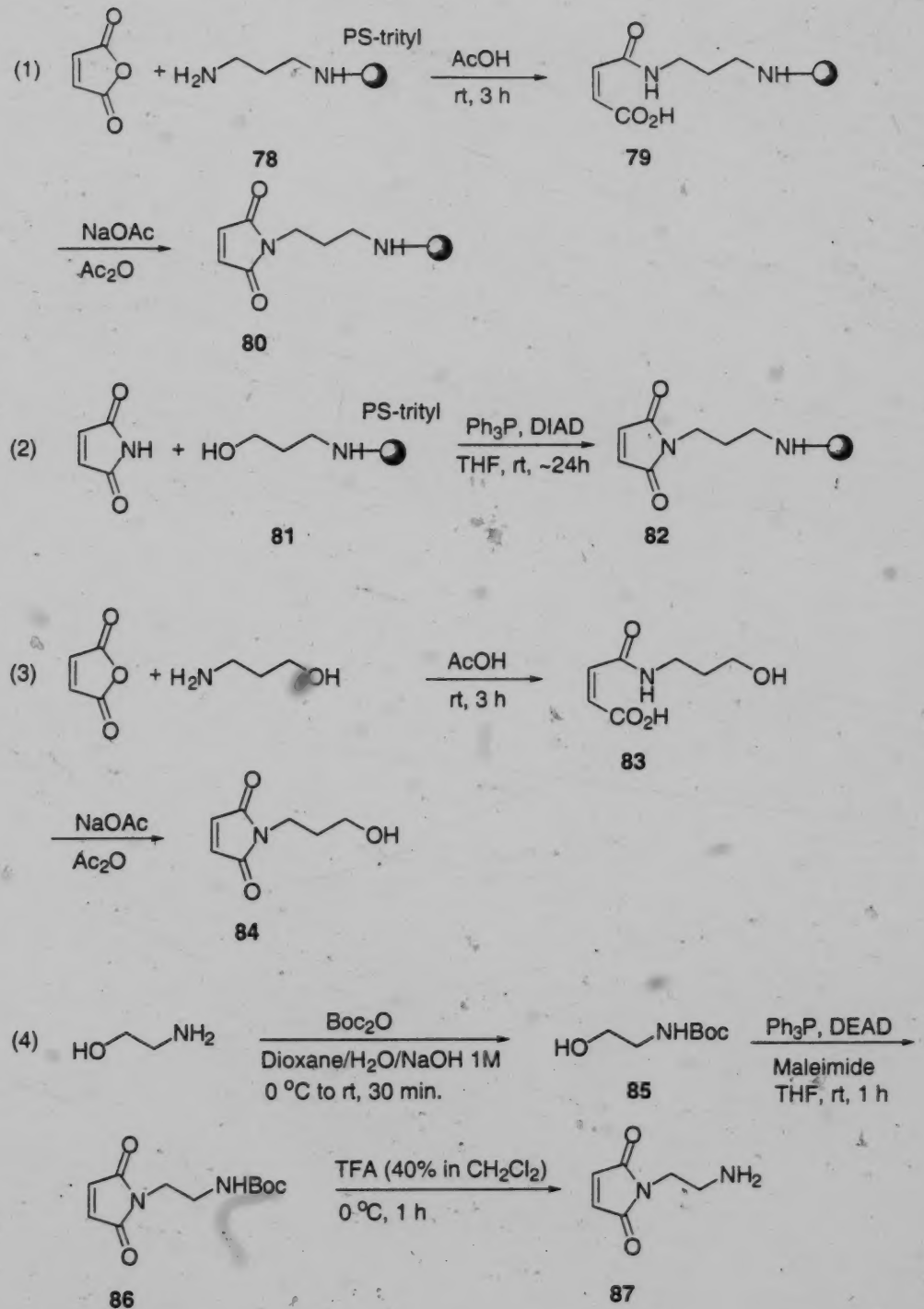
Scheme 25



Scheme 26



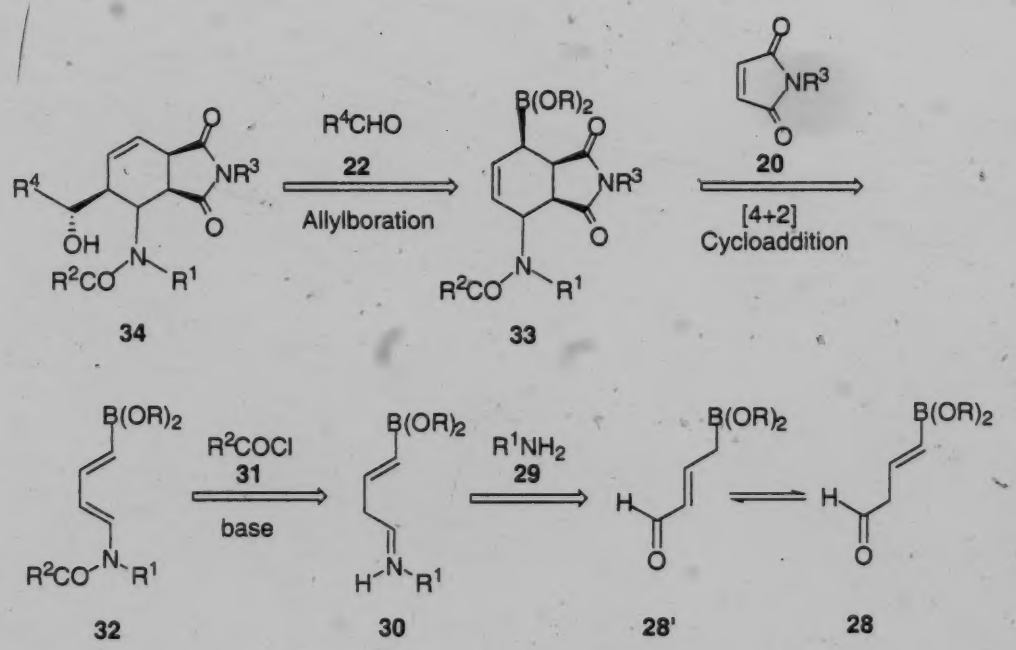
Scheme 27


(1)
PS-trityl
AcOH
rt, 3 h
78
79
NaOAc
Ac2O
80
(2)
PS-trityl
Ph3P, DIAD
THF, rt, ~24h
81
82
(3)
AcOH
rt, 3 h
83
NaOAc
Ac2O
84
(4)
Boc2O
Dioxane/H2O/NaOH 1M
0 °C to rt, 30 min.
85
Ph3P, DEAD
Maleimide
THF, rt, 1 h
TFA (40% in CH2Cl2)
0 °C, 1 h
86
87

C. Optimization of the acylaminobutadiene route.

We have also explored the scope of the tandem [4+2]/allylboration methodology using acylaminobutadienes (X=C, Scheme 5). This route is based on Oppolzer's original work.[17] As shown in Scheme 5 reproduced in the next page , it requires the homologous aldehyde precursor **28** and would eventually lead to bicyclic systems of type **34**.

Scheme 5

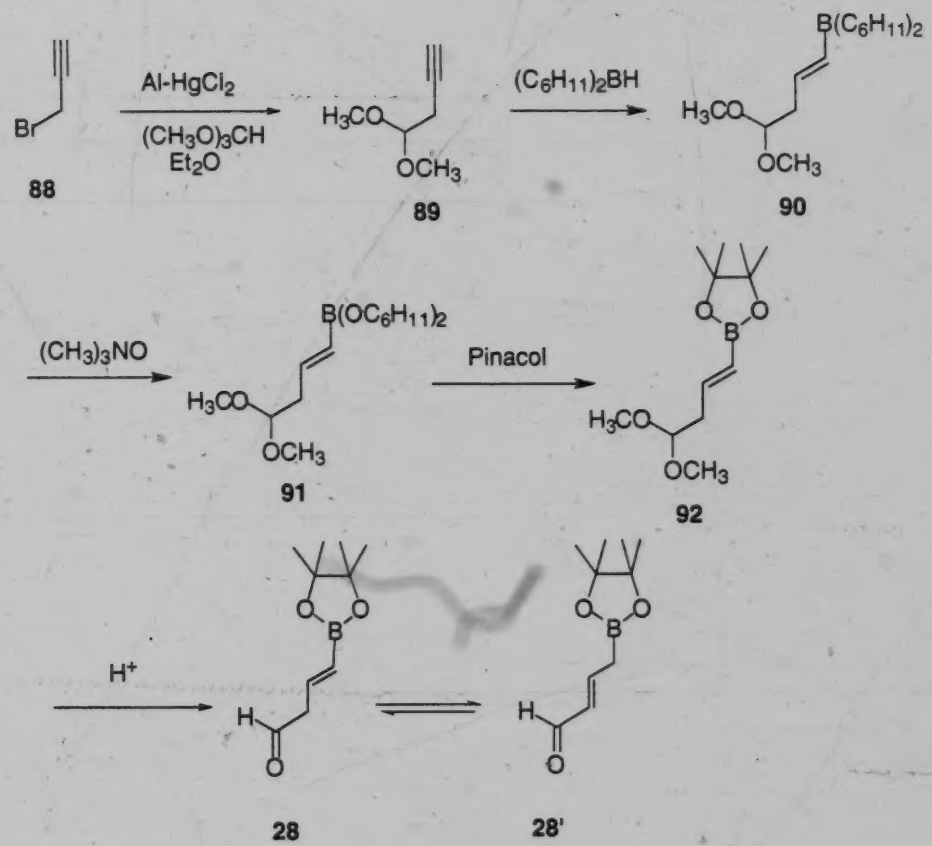


The required homologous acetal **89** is not commercially available (Scheme 28). It can be made by reacting propargyl bromide with dialkyl orthoformate in the presence of either oganoaluminium compounds or Grignard reagents. However, according to literature reports,[35] organomagnesium compounds display low reactivity with orthoformates. The reaction is usually incomplete and separation of the pure acetal is sometimes very difficult. In most cases, the required acetal **89** is prepared by using aluminium-mercuric chloride compounds. We followed the literature procedure described by Michael Jung et al.[34] We encountered several problems while attempting this procedure. The reaction was found to be sensitive to the quality of the aluminium being used. It was also impossible to separate the pure acetal from the reaction solvent. We tried this reaction several times using different batches of aluminium and orthoformates. According to literature reports,[35] the acetal could be easily prepared from the aluminium derivative of an unsaturated bromide using the mixed orthoformate $C_6H_5O\text{-}CH(OC_2H_5)_2$. The increased reactivity of the mixed orthoformate is due to the phenoxyl group, which is a better leaving group than an alkoxyl group. Yet we discovered that this reaction never went to completion. However, we finally managed to make the reaction work by pre-stirring the aluminium in diethyl ether at 50 °C for 12 h to activate the aluminate

surface. In this manner, with diethyl ether as reaction solvent, we obtained the pure acetal **89** in 45% yield. In order to achieve the desired transformation, acetal **89** was hydroborated-using dicyclohexylborane followed by oxidation using two equivalents of trimethylamine *N*-oxide dihydrate. Subsequent transesterification with pinacol gave **92** in 45% yield. The acetal was removed by acid-catalyzed transacetalization using acetone, affording the required aldehyde **28** along with its enal form **28'**. Unfortunately, this reaction never went to completion and we observed the desired aldehyde **28** with a significant proportion of unreacted **92**. We used an excess of acid and a longer reaction time to drive the reaction to completion. After two hours, ^{1}H NMR showed completion of the reaction. However, in a model reaction, treatment of **28** with benzylamine followed by acetylation failed to give the desired acylaminodiene. We tried to reproduce a simpler example from Oppolzer's original reports lacking the boronic ester substituent in order to confirm our technique and/or a possible substrate incompatibility. The imine **95** was prepared by condensation of crotonaldehyde **93** with benzyl amine (**94**). Acylation of the imine using benzoyl chloride **96** in the presence of triethylamine in toluene provided the expected dienamide **97** in 70% yield. However, compound **28** failed to give the desired dienamide adduct under similar conditions. Hence, believing that the

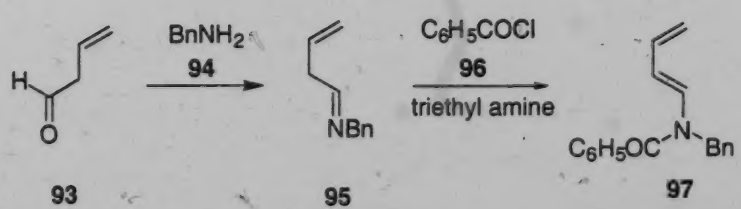
problem may lie in the degradation of **28** under the reaction conditions, we abandoned this approach.

Scheme 28



88 89 90 91 92 28 28'

Scheme 29



93 95 97

III. CONCLUSION

In summary, we developed a new multicomponent reaction for the preparation of cyclic β-amino alcohol derivatives that employs 1-aza-4-borono-butadienes, maleimides, and aldehyde components. This tandem [4+2]/allylboration described herein offers several advantages. First, this method provides access to nitrogen-containing bicyclic compounds such as **43**, which can be useful intermediates in the synthesis of α-hydroxyalkyl piperidine derivatives. Second, the amino groups in **43** provide an opportunity for the introduction of chirality onto the diene structure, allowing an extension of this methodology to asymmetric synthesis. Another attractive feature of this tandem process is the simple addition of all starting materials at once, without the need of adding any external reagents, leading to bicyclic products with four stereogenic centers and four variable groups in one operation. If this reaction functions well on solid-phase, this procedure will allow the synthesis of relevant small molecule libraries. In principle, compounds of type **53f** could be easily transformed into numerous other amines and amino acids and eventually cyclized to give tricyclic product **74**. Moreover, the stereochemistry of the resulting β-amino alcohol unit is the same as

that of several alkaloids, such as methyl palustramate, swainsonine and castanospermine (Figure 3), thus confirming the potential of this strategy for natural product synthesis. The mild conditions involved in this new methodology are well suited for the production of combinatorial libraries by manual or automated methods. The scope of this reaction and its applications are still under investigation by our laboratory.

IV. EXPERIMENTAL

General

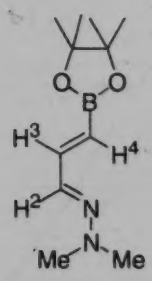
Unless otherwise noted, all operations were carried out in oven or flame-dried glassware under a dry, oxygen-free nitrogen atmosphere. Acetone, CH_2Cl_2, cyclohexene, DME, EtOH, Et_2O, MeOH and toluene were freshly distilled from calcium hydride prior to use. Anhydrous THF was distilled from sodium in a recycling still. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Pinacol was recrystallized from benzene and dried under vacuum. All organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated with a rotary evaporator under reduced pressure. Chromatography refers to flash column chromatography on silica gel (230-400 mesh) obtained from Silicycle, Quebec. Thin-layer chromatography (TLC) was performed on 0.25 mm Merck precoated silica plates (60F-254). Visualization was obtained by short wave UV light and exposure to 5% phosphomolybdic acid in ethanol. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz in $CDCl_3$ as solvent unless otherwise mentioned. Proton chemical shifts are

expressed in parts per million (ppm) and recorded relative to tetramethylsilane as an internal standard. Coupling constants are expressed as *J* values in hertz units with error margin of ±0.5 Hz. The following abbreviation are used: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH-300 (75 MHz) NMR spectrometer in $CDCl_3$ as solvent, and chemical shifts are expressed in ppm. Nuclear Overhauser enhancement (NOE) experiment was recorded at 500 MHz in $CDCl_3$ as solvent. A sample for NOE measurement was deoxygenated by passing nitrogen through the deuterated solution for 5 minutes. Two-dimensional (2D) homonuclear correlation spectrum (COSY) was performed on a Bruker WH-300 MHz NMR spectrometer. Infrared spectra were obtained on a Nicolet Magna-IR™ 750. Frequencies are expressed in cm^{-1}. Melting points were determined in a capillary tube on a Gallenkamp melting point instrument and are uncorrected. HPLC of **53a** and **53b** was performed on a Zorbax SB-C18 column (4.6 × 150 mm, 5 μm) by using 40% acetonitrile/water as eluent. Elemental analyses (C, H, N) were performed by the microanalytical laboratory of our department. High resolution electrospray mass spectra (HRMS) were obtained on a Micromass ZabSpec oa TOF instrument. Significant protonated molecular ions $(M+H)^+$ as well as peaks

corresponding to sodiated molecular ions $(M+Na)^+$ were present in most of the spectra, due to trace amounts of sodium salts in the samples. X-ray analysis was performed on Bruker SMART 1000/P4/RA diffractometer by Dr. R. MacDonald at the University of Alberta.

Preparation of dienes 50.

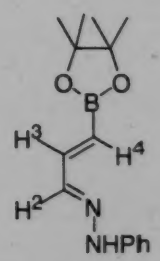
***N,N*-Dimethylamino-1-aza-4-borono-1,3-butadiene (50a).**



To a solution of *N,N*-dimethylhydrazine (0.49 mL, 6.50 mmol, 1 equiv) and sodium hydrogen phosphate (0.923 g, 6.50 mmol, 1 equiv) in water (2 mL), a solution of α,β-unsaturated carbonyl compound **39** (1.183 g, 6.50 mmol, 1 equiv) in anhydrous Et_2O (10 mL) was added. After vigorous stirring of the mixture for 30 minutes at 50 °C, the mixture was extracted three times with ether (25 mL each). These

extracts were dried over anhydrous magnesium sulfate and evaporated to give **50a** (0.992 g, 70%) as pale yellow oil. This compound was used for the next reaction without further purification. Spectroscopic data for **50a**: IR ($CHCl_3$ cast) 2977, 2931, 2865, 1548, 1412, 1213, 998, 882, 779, 481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.9, 17.9 Hz, 1H, H^3), 6.93 (d, J = 8.9 Hz, 1H, H^2), 5.53 (d, J = 17.9 Hz, 1H, H^4), 2.95 (s, 6H, N-N(CH_3)$_2$), 1.22 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$, APT) δ 148.2 (CH), 135.6 (CH), 134.5 (CH), 83.0 (C), 42.4 (N-CH_3), 24.9 (CH_3); MS (ES) *m/z* 225 $(M+H)^+$; HRMS (ES) *m/z* calcd. for $C_{11}H_{22}B_1N_2O_2$ $(M+H)^+$ 225.1774, found 225.1778.

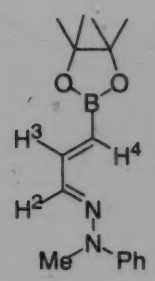
_N_-phenylamino-1-aza-4-borono-1,3-butadiene (50f).



To a solution of *N*-phenylhydrazine (0.280 mL, 2.849 mmol, 1 equiv) and sodium hydrogen phosphate (0.404 g, 2.849 mmol, 1 equiv) in water (1 mL), a solution of α,β-unsaturated carbonyl compound **39** (0.519 g, 2.849 mmol, 1 equiv) in anhydrous Et_2O (6

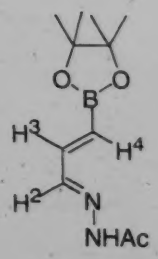
mL) was added. After vigorous stirring of the mixture for 30 minutes at 50 °C, the mixture was extracted three times with ether (10 mL each). These extracts were dried over anhydrous magnesium sulfate and evaporated to give **50f** (0.666 g, 86%) as pale yellow oil. This compound was used for the next reaction without further purification. Spectroscopic data for **50f**: IR ($CHCl_3$ cast) 3285, 2977, 2924, 1560, 1446, 1286, 1214, 1070, 899, 648, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.34 (m, 5H), 6.99 (d, J = 9.0 Hz, 1H, H^2), 6.87 (dd, J = 9.0, 18.0 Hz, 1H, H^3), 5.68 (d, J = 18.0 Hz, 1H, H^4), 1.25 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$, APT) δ 146.4 (CH), 139.9 (CH), 129.2 (CH), 120.4 (CH), 120.6 (CH), 112.1 (CH), 143.9 (C), 82.7 (C), 24.7 (CH_3); MS (ES) *m/z* 305 $(M+Na)^+$, 273 $(M+H)^+$; HRMS (ES) *m/z* calcd. for $C_{15}H_{22}B_1N_2O_2$ $(M+H)^+$ 273.1774, found 273.1769.

_N_-Methyl-_N_-phenylamino-1-aza-4-borono-1,3-butadiene (50g).



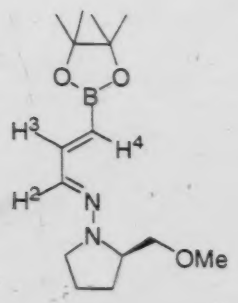
To a solution of 1-methyl-1-phenylhydrazine (0.332 mL, 2.817 mmol, 1 equiv) and sodium hydrogen phosphate (0.400 g, 2.817 mmol, 1 equiv) in water (1 mL), a solution of α,β-unsaturated carbonyl compound **39** (0.513 g, 2.817 mmol, 1 equiv) in anhydrous Et_2O (6 mL) was added. After vigorous stirring of the mixture for 30 minutes at 50 °C, the mixture was extracted three times with ether (10 mL each). These extracts were dried over anhydrous magnesium sulfate and evaporated to give **50g** (0.645 g, 81%) as pale yellow oil. This compound was used for the next reaction without further purification. Spectroscopic data for **50g**: IR ($CHCl_3$ cast) 2977, 2926, 1651, 1611, 1552, 1457, 1215, 1030, 897, 668, 646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, APT) δ 7.25 (m, 5H), 6.89-6.98 (m, 2H, H^2, H^3), 5.70 (d, 1H, J = 15.3 Hz, H^4), 3.34 (s, 3H, NCH_3), 1.26 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$, APT) δ 148.4 (CH), 135.7 (CH), 128.8 (CH), 118.4 (CH), 115.6 (CH), 114.8 (CH), 152.6 (C), 83.1 (C), 44.3 (N-CH_3), 24.7 (CH_3); MS (ES) *m/z* 287 $(M+H)^+$; HRMS (ES) *m/z* calcd. for $C_{16}H_{24}B_1N_2O_2$ $(M+H)^+$ 287.1931, found 287.19.

***N*-Acylamino-1-aza-4-borono-1,3-butadiene (50h).**



To a solution of α,β-unsaturated carbonyl compound **39** (1.010 g, 5.549 mmol, 1 equiv) in anhydrous EtOH (20 mL), acetic hydrazide (0.411 g, 5.549 mmol, 1 equiv) was added. After vigorous stirring of the mixture for 1 h at 85 °C, the mixture was evaporated and dried over vacuum to give **50h** as pale yellow solid. The crude product was subjected to flash chromatography on silica gel, eluting with 10% MeOH in dichloromethane, to give **50h** (0.819 g, 62%). Spectroscopic data for **50h**: IR ($CHCl_3$ cast) 3205, 2978, 1958, 1618, 1560, 1270, 1214, 898, 667, 649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 9.1 Hz, 1H, H^2), 7.06 (dd, J =8.8, 18.0 Hz, 1H, H^3), 5.92 (d, J = 18.0 Hz, 1H, H^4), 3.47 (s, 3H, $COCH_3$), 1.23 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$, APT) δ 174.3 (CO), 146.2 (CH), 146.5 (CH), 145.0 (CH), 83.7 (C), 24.8, 20.2 (CH_3); MS (ES) *m/z* 261 $(M+Na)^+$, 239 $(M+H)^+$; HRMS (ES) *m/z* calcd. for $C_{11}H_{20}B_1N_2O_3$ $(M+H)^+$ 239.1567, found 239.1564.

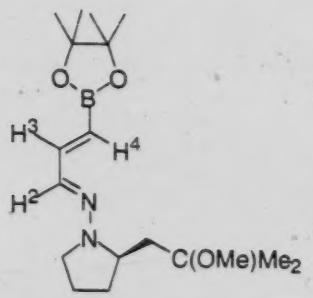
***N*-[(S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine]-1-aza-4-borono-1,3-butadiene (66a).**



α,β-Unsaturated carbonyl compound **39** (0.271 g, 1.489 mmol, 1 equiv) was dissolved in anhydrous Et_2O (10 mL). The resulting solution was cooled at 0 °C. Catalytic amount of acetic acid was added to the above solution followed by addition of SAMP (0.385 g, 2.978 mmol, 2 equiv). After vigorous stirring of the mixture for 1 h at 50 °C, the mixture was extracted two times with H_2O (10 mL each). All the organic layers were combined and washed with saturated aqueous sodium chloride solution once. These extracts were dried over anhydrous magnesium sulfate and evaporated to give **66a** (0.347 g, 79%) as pale yellow solid. This compound was used for the next reaction without further purification. Spectroscopic data for **66a**: IR ($CHCl_3$ cast) 2976, 2925, 1606, 1546, 1455, 1270, 1197, 997, 900, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, J = 9.0, 18.0 Hz, 1H,

H^3), 6.91 (d, J = 9.0 Hz, 1H, H^2), 5.50 (d, J = 18.0 Hz, 1H, H^4), 3.62 (m, 1H, CHN), 3.21-3.59 (m, 5H, $\mathbf{CH_2OCH_3}$), 1.41-1.99 (m, 6H, CH_2), 1.25 (m, 12H); ^{13}C NMR (300 MHz, $CDCl_3$, APT) δ 148.6 (CH), 148.6 (CH), 134.6 (CH), 62.7 (CH), 83.0 (C), 74.2 ($\mathbf{CH_2OCH_3}$), 48.3 (CH_2), 24.9 (CH_2), 22.2 (CH_2), 59.9 (CH_3O), 24.8 (CH_3); MS (ES) m/z 318 $(M+Na)^+$, 295 $(M+H)^+$; HRMS (ES) m/z calcd. for $C_{15}H_{27}B_1N_2O_3K$ $(M+K)^+$ 333.1752, found 333.1754.

N-[(S)-(-)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine]-1-aza-4-borono-1,3-butadiene (66b).

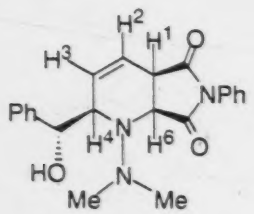


α,β-Unsaturated carbonyl compound **39** (0.346 g, 1.901 mmol, 1 equiv) was dissolved in anhydrous Et_2O (20 mL). The resulting solution was cooled at 0 °C. Catalytic amount of acetic acid was added to the above solution followed by addition of SADP (0.602 g, 3.802 mmol, 2 equiv). After vigorous stirring of the mixture for 1 h at 50 °C, the mixture was extracted two times with H_2O (10 mL each).

All the organic layers were combined and washed with saturated aqueous sodium chloride solution once. These extracts were dried over anhydrous magnesium sulfate and evaporated to give **66b** (0.571 g, 93%) as pale yellow solid. This compound was used for the next reaction without further purification. Spectroscopic data for **66b**: IR ($CHCl_3$ cast) 2975, 2933, 2826, 1468, 1213, 924, 667, 647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (dd, J = 9.1, 17.9 Hz, 1H, H^3), 6.93 (d, J =8.9, 1H, H^2), 5.46 (d, J = 17.9 Hz, 1H, H^4), 3.31-3.43 (m, 1H, CHN), 3.21 (s, 3H, OCH_3), 2.20-2.50 (m, 2H, CH_2N), 1.53-1.91 (m, 4H, CH_2), 1.23 (s, 12H), 1.12 (d, 6H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$, APT) δ 149.4 (CH), 148.9 (CH), 135.1 (CH), 76.0 (CH), 83.3 (C), 82.3 (C), 48.9 (CH_2) , 26.7 (CH_2), 21,7 (CH_2), 23.2 (OCH_3), 22.0 (CH_3), 22.1 (CH_3), 19.4 (CH_3); MS (ES) *m/z* 323 $(M+H)^+$; HRMS (ES) *m/z* calcd. for $C_{17}H_{32}B_1N_2O_3$ $(M+H)^+$ 323.2506, found 323.2500.

Preparation of Bicyclic alcohols 53.

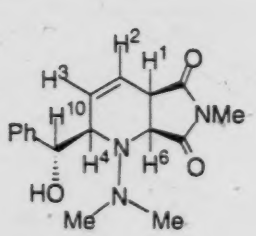
(1R,4R,6S,10R)-5-Dimethylamino-4-α-hydroxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53a).



To a solution of diene **50a** (0.550 g, 2.455 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.260 mL, 2.46 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.850 g, 4.911 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (15 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53a** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **53a** (0.434 g, 47%) as pale yellow solid;

mp 80-82 °C. Spectroscopic data for **53a**: IR ($CHCl_3$ cast) 3475, 2944, 1783, 1597, 1454, 1199, 1059, 864, 667, 646, 621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.55 (m, 10H), 6.01 (ddd, J = 1.5, 3.7, 10.6 Hz, 1H, H^3), 5.75 (ddd, J = 1.5, 4.3, 10.6 Hz, 1H, H^2), 4.62 (d, J = 8.4 Hz, 1H, H^6), 4.24 (br s, 1H, OH), 3.89 (d, J = 9.5 Hz, 1H, C^{10}), 3.52-3.63 (m, 2H, H^1, H^4), 2.50 (s, 6H, N-N$(CH_3)_2$); ^{13}C (300 MHz, $CDCl_3$, APT) δ: 176.1 (CO), 174.9 (CO), 140.1 (C), 131.6 (C), 130.6 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.2 (CH), 126.3 (CH), 121.1 (CH), 76.6 (CH), 61.4 (CH), 57.2 (CH), 38.9 (CH), 43.7 [N-N$(CH_3)_2$]; MS (ES) *m/z* 400 $(M+Na)^+$; HRMS (ES) *m/z* calcd. for $C_{22}H_{23}N_3O_3Na$ $(M+Na)^+$ 400.1637, found 400.1639.

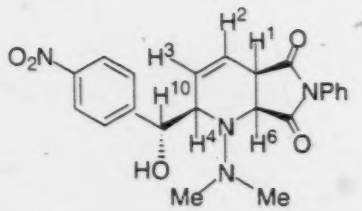
(1R,4R,6S,10R)-5-Dimethylamino-4-α-hydroxybenzyl-8-methyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53b).



To a solution of diene **50a** (0.580 g, 2.589 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.263 mL, 2.589 mmol, 1

equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-methylmaleimide (0.575 g, 5.179 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted several times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53b** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **53b** (0.408 g, 50%) as pale yellow solid; mp 110-112 °C. Spectroscopic data for **53b**: IR ($CHCl_3$ cast) 3463, 2945, 1779, 1704, 1454, 1434, 1279, 1199, 1124, 990, 809, 775, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.32 (m, 5H), 5.92 (ddd, J = 1.6, 3.6, 10.6 Hz, 1H, H^3), 5.66 (ddd, J = 2.1, 4.4, 10.6 Hz, 1H, H^2), 4.42 (d, J = 8.5 Hz, 1H, H^6), 4.26 (br s, 1H, OH), 3.73 (d, J = 9.6 Hz, 1H, C^{10}), 3.40-3.46 (m, 2H, H^1, H^4), 3.05 (s, 3H, N-CH_3) 2.46 (s, 6H, N-N(CH_3)$_2$); ^{13}C (300 MHz, $CDCl_3$, APT) δ 177.0 (CO), 175.1 (CO), 140.2 (C), 130.2 (CH), 128.4 (CH), 128.1 (CH), 127.1 (CH), 121.2 (CH), 75.6 (CH), 61.2 (CH), 57.3 (CH), 38.7 (CH), 43.7 [N-N(CH_3)$_2$], 25.3 (N-CH_3); MS (ES) *m/z* 338 $(M+Na)^+$, 316 $(M+H)^+$; HRMS (ES) *m/z* calcd for $C_{17}H_{21}N_3O_3Na$ $(M+Na)^+$ 338.1481, found 338.1481.

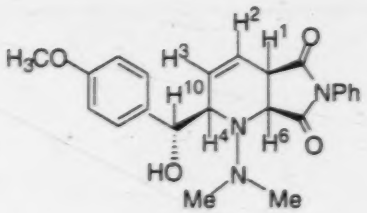
(1R,4R,6S,10R)-5-Dimethylamino-4-α-hydroxy-*p*-nitrobenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53c).



To a solution of diene **50a** (0.100 g, 0.446 mmol, 1 equiv) in toluene (5 mL) was added *o*-nitrobenzaldehyde (0.068 mL, 0.446 mmol, 1equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.155 g, 0.893 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53c** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **53c** (0.090 g, 48%) as pale yellow solid; mp 90-92 °C. Spectroscopic data for **53c**: IR ($CHCl_3$

cast) 3439, 2922, 2852, 1778, 1597, 1499, 1376, 1197, 1108, 1072, 752, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2H), 7.24-7.54 (m, 7H), 6.10 (ddd, J = 1.4, 3.8, 10.6 Hz, 1H, H^3), 5.75 (ddd, J = 2.2, 5.3, 10.2 Hz, 1H, H^2), 4.62 (d, J = 8.9 Hz, 1H, H^6), 4.31 (br s, 1H, OH), 4.02 (d, J = 9.6 Hz, 1H, C^{10}), 3.59 (m, 1H, H^4), 3.39 (m, 1H, H^1), 2.49 (s, 6H, N-N(CH_3)$_2$); ^{13}C (300 MHz, $CDCl_3$, APT) δ 176.1 (CO), 176.0 (CO), 147.8 (C), 147.7 (C), 131.4 (C), 131.4 (CH), 129.4 (CH), 129.2 (CH), 126.5 (CH), 126.2 (CH), 123.6 (CH), 122.1 (CH), 76.1 (CH), 62.1 (CH), 56.2 (CH), 38.9 (CH), 43.5 [N-N(CH_3)$_2$]; MS (ES) m/z 445 $(M+Na)^+$, 423 $(M+H)^+$; HRMS (ES) m/z Calcd for $C_{22}H_{22}N_4O_5Na$ $(M+Na)^+$ 445.1488, found 445.1482.

(1R,4R,6S,10R)-5-Dimethylamino-4-α-hydroxy-*p*-methoxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53d).

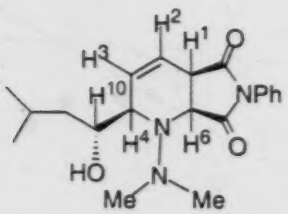


To a solution of diene **50a** (0.187 g, 0.833 mmol, 1 equiv) in toluene (5 mL) was added *p*-methoxybenzaldehyde (0.101 mL, 0.833

mmol, 1equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.289 g, 1.666 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53d** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **53d** (0.176 g, 52%) as pale yellow solid; mp 107-110 °C. Spectroscopic data for **53d**: IR ($CHCl_3$ cast) 3476, 2919, 2850, 1651, 1597, 1513, 1302, 1137, 832, 806, 692, 405 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.49 (m, 7H), 6.87 (d, 2H), 5.98 (ddd, J = 1.5, 3.7, 10.5 Hz, 1H, H^3), 5.73 (ddd, J = 2.2, 4.5, 10.5 Hz, 1H, H^2), 4.60 (d, J = 8.4 Hz, 1H, H^6), 3.86 (d, J = 9.1 Hz, 1H, C^{10}), 3.76 (s, 3H, OCH_3), 3.57 (m, 1H, H^4), 3.48 (m, 1H, H^1), 2.45 (s, 6H, N-N(CH_3)$_2$); ^{13}C (300 MHz, $CDCl_3$, APT) δ 176.0, 174.0 (CO), 159.6, 132.1, 131.6 (C), 130.7, 129.3, 128.9, 128.3, 126.2, 121.1, 113.9, 75.6, 61.5, 57.2, 55.3 (CH), 38.8 (OCH_3), 43.7 [N-N(CH_3)$_2$]; MS (ES) *m/z* 430 $(M+Na)^+$, 408 $(M+H)^+$, 390 $(M-H_2O)^+$;

HRMS (ES) *m/z* calcd for $C_{23}H_{25}N_3O_4Na$ $(M+Na)^+$ 430.1743, found 430.1742.

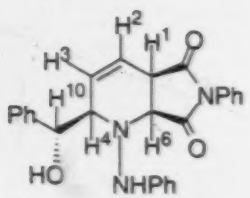
(1R,4R,6S,10R)-5-Dimethylamino-4-α-hydroxyisobutyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53e).



To a solution of diene **50a** (0.108 g, 0.481 mmol, 1 equiv) in toluene (5 mL) was added isovaleraldehyde (0.052 mL, 0.481 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.167 g, 0.962 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53e** as a crude product. Purification by flash column

chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **53e** (0.085 g, 50%) as pale yellow solid; mp 75-78 °C. Spectroscopic data for **53e**: IR ($CHCl_3$ cast) 2953, 1777, 1713, 1597, 1499, 1455, 1383, 1180, 751, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.58 (m, 5H), 6.17 (dddd, J = 0.9, 2.2, 4.6, 8.4 Hz, 1H, H^3), 6.04 (ddd, J = 2.1, 4.0, 10.5 Hz, 1H, H^2), 4.52 (d, J = 8.6 Hz, 1H, H^6), 3.54 (m, 1H, C^{10}), 3.24 (m, 2H, H^1, H^4), 2.49-2.51 (s, 8H, N-N$(CH_3)_2$, **CH_2**-CH), 1.91 (m, 1H, **CH**-$(CH_3)_2$), 0.92 (s, 6H, CH_3); ^{13}C (300 MHz, $CDCl_3$, APT) δ 176.4 (CO), 174.1 (CO), 131.6 9 (C), 130.9 (CH), 129.2 (CH), 129.2 (CH), 126.2 (CH), 121.2 (CH), 70.7 (CH), 60.0 (CH), 57.4 (CH), 57.2 (CH), 43.7 (CH), 42.4 (CH_2), 38.6 [N-N$(CH_3)_2$], 24.6 (CH_3), 23.9 (CH_3); MS (ES) *m/z* 380 $(M+Na)^+$, 358 $(M+H)^+$; HRMS (ES) *m/z* calcd for $C_{20}H_{28}N_3O_3$ $(M+H)^+$ 358.2131, found 358.2136.

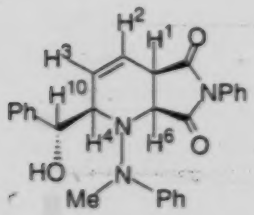
(1R,4R,6S,10R)-5-Phenylamino-4-α-hydroxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53f).



To a solution of diene **50f** (0.111 g, 0.406 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.041 mL, 0.406 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.141 g, 0.813 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53f** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **53f** (0.081 g, 46%) as pale yellow solid; mp 180-182 °C. Spectroscopic data for **53f**: IR ($CHCl_3$ cast) 3515, 3028, 2920, 1715, 1600, 1495, 1454, 1384, 1371, 1247, 1195, 1058, 971, 828, 751, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-6.92 (m, 15H), 6.19 (m, 1H, H^3), 5.69 (br s, 1H, NH), 5.59 (ddd, J = 2.2, 4.4, 10.4 Hz, 1H, H^2), 4.61 (d, J = 9.2 Hz, 1H, H^6), 4.22 (d, J = 9.6 Hz, 1H, C^{10}), 3.91 (br s, 1H, OH), 3.73 (m, 2H, H^1, H^4); ^{13}C (300 MHz, CD_2Cl_2, CPD) δ 173.6 (CO), 173.5 (CO), 147.1 (C), 139.4, 131.3 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 127.1 (CH), 126.2 (CH), 126.1 (CH), 121.1 (CH), 114.1 (CH),

76.3 (CH), 68.1 (CH), 38.3 (CH); MS (ES) *m/z* 448 $(M+Na)^+$; HRMS (ES) *m/z* calcd for $C_{26}H_{23}N_3O_3Na$ $(M+Na)^+$ 448.1637, found 448.1636. Anal. Calcd: C, 73.5; H, 5.4; N, 9.9. Found: C, 73.2; H, 5.2; N, 9.6.

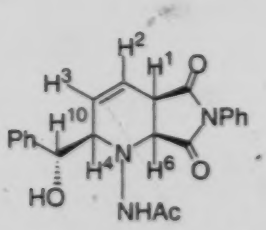
(1R,4R,6S,10R)-5-(*N*-Methyl-*N*-phenylamino)-4-α-hydroxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53g).



To a solution of diene **50g** (0.439 g, 1.535 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.156 mL, 1.535 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.532 g, 3.071mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53g**

as a crude product. Purification by flash column chromatography using 20% EtOAc in hexane led to the isolation of the pure alcohol **53g** (0.310 g, 46%) as pale yellow solid; mp 190-192 °C. Spectroscopic data for **53g**: IR ($CHCl_3$ cast) 3497, 2921, 1716, 1597, 1496, 1454, 1384, 1371, 1244, 1141, 971, 829, 792, 692, 622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 15H), 6.10 (ddd, J = 1.5, 3.5, 10.6Hz, 1H, H^3), 5.81 (ddd, J = 2.4, 4.1, 10.6 Hz, 1H, H^2), 4.41 (d, J = 8.3 Hz, 1H, H^6), 4.20 (d, J = 8.9 Hz, 1H, C^{10}), 3.96 (br s, 1H, OH), 3.71-3.62 (m, 2H, H^1, H^4), 3.01 (s, 3H, CH_3); ^{13}C (300 MHz, $CDCl_3$) δ 175.7 (CO), 173.6 (CO), 149.3 (C), 139.8 (C), 131.4 (C), 131.4 (CH), 131.0 (CH), 129.5 (CH), 129.3 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 127.2 (CH), 126.1 (CH), 120.1 (CH), 114.4 (CH), 76.6 (CH), 66.3 (CH), 58.6 (CH), 39.5 (CH), 35.6 (CH_3); MS (ES) *m/z* 462 $(M+Na)^+$; HRMS (ES) *m/z* calcd for $C_{27}H_{25}N_3O_3Na$ $(M+Na)^+$ 462.1794, found 462.1792.

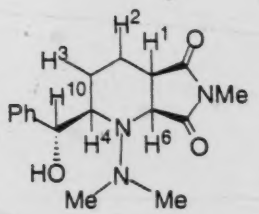
(1R,4R,6S,10R)-5-Acylamino-4-α-hydroxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (53h).



To a solution of diene **50h** (0.124 g, 0.523 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.053 mL, 0.523 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.181 g, 1.044 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **53h** as a crude product. Purification by flash column chromatography using 20% EtOAc in hexane led to the isolation of the pure alcohol **53h** (0.086 g, 42%) as pale yellow solid; mp 110-112 °C. Spectroscopic data for **53h**: IR ($CHCl_3$ cast) 3021, 2960, 2924, 2852, 1593, 1567, 1496, 1455, 1371, 1259, 1229, 1186, 1153, 1100, 1026, 920, 867, 793, 730, 667, 620, 510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 10H), 6.10 (ddd, J = 2.2, 3.0, 10.4 Hz, 1H, H^3), 5.98 (ddd, J = 2.4, 3.5, 10.4 Hz, 1H, H^2), 5.82 (d, J = 5.5 Hz, 1H, H^6), 5.22 (d, J = 9.3 Hz, 1H, C^{10}), 4.72 (m, 1H, H^4), 3.81 (m, 1H, H^1), 1.92 (s, 3H, OCH_3); ^{13}C (300 MHz, $CDCl_3$, APT) δ 174.0 (CO), 173.4 (CO), 169.6 (CO), 136.9 (C), 136.0 (C), 131.4 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.4 (CH), 121.0

(CH), 77.5 (CH), 61.8 (CH), 58.7 (CH), 39.8 (CH), 21.1 ($COCH_3$); MS (ES) *m/z* 414 $(M+Na)^+$; HRMS (ES) *m/z* calcd for $C_{22}H_{21}N_3O_4Na$ $(M+Na)^+$ 414.1430, found 414.1430.

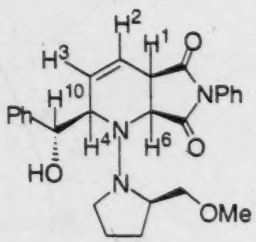
(1R,4R,6S,10R)-5-Dimethylamino-4-α-hydroxybenzyl-8-methyl-5,8-diazabicyclo [4.3.0] nonane-7,9-dione (58).



To a suspension of 10% Pd on carbon (0.160 g) in EtOH (3 mL), under an H_2 atmosphere, was added **53b** previously prepared (0.160 mg, 0.509 mmol) in EtOH (2 mL). After 18 h of stirring at rt, the catalyst was filtered out. The solution was concentrated and chromatographed on silica gel (5% MeOH in dichloromethane) affording 0.127 g (75% yield) of **58** as pale yellow solid, which was crystallized from dichloromethane at rt; mp 138-140 ^{0}C. Spectroscopic data for **58**: IR ($CHCl_3$ cast) 3018, 2916, 2848, 1704, 1434, 1383, 1282, 1215, 1130, 1062, 967, 754, 702, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.34 (m, 5H), 4.36 (d, J = 8.8 Hz,

1H, H^6), 3.98 (d, J = 7.2 Hz, 1H, C^{10}), 2.95-3.08 (m, 5H, N-CH_3, H^1, H^4), 2.45 [s, 6H, N-N$(CH_3)_2$], 1.95 (m, 1H, H^3), 1.67 (m, 1H, H^3), 1.20 (m, 1H, H^2), 0.87 (m, 1H, H^2); ^{13}C (300 MHz, $CDCl_3$, APT) δ 178.6 (CO), 178.3 (CO), 142.1 (C), 128.2 (CH), 127.5 (CH), 126.9 (CH), 78.7 (CH), 65.2 (CH), 51.8 (CH), 40.4 (CH), 22.8 (CH_2), 21.7 (CH_2), 42.1 [N-N$(CH_3)_2$], 25.17 (NCH_3); MS (ES) m/z 340 $(M+Na)^+$, 318 $(M+H)^+$; HRMS (ES) m/e calcd for $C_{17}H_{23}N_3O_3Na$ $(M+Na)^+$ 340.1637, found 340.1635.

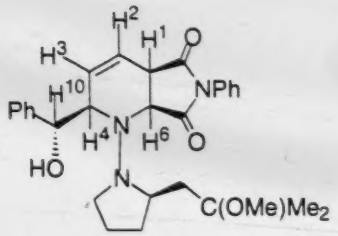
(1R,4R,6S,10R)-5-[(S)-(-)-1-amino-2(methoxymethyl)pyrrolidine]-4-α-hydroxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (67a).



To a solution of diene **66a** (0.347 g, 1.180 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.120 mL, 1.180 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (0.409 g, 2.361 mmol, 2 equiv) was added to the above solution and heated at

80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **67a** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **67a** (0.232 g, 44% yield) as pale yellow solid; mp 73-75 °C. Spectroscopic data for **67a**: IR ($CHCl_3$ cast) 3373, 2924, 1715, 1597, 1498, 1455, 1384, 1371, 1197, 1144, 972, 911, 850, 753, 692, 667, 622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.62-7.12 (m, 10H), 6.02 (ddd, J = 1.3, 3.8, 9.6 Hz, 1H, H^3), 5.68 (ddd, J = 2.3, 4.7, 9.6 Hz, 1H, H^2), 4.72 (d, J = 8.6, 1H, H^6), 4.02 (d, J = 9.6, 1H, C^{10}), 3.62 (m, 2H), 3.60 (s, 3H, OCH_3), 3.21-3.41 (m, 3H, $\mathbf{CH_2}OCH_3$, CHN), 2.20-2.49 (m, 2H, CH_2N), 1.51-1.92 (m, 4H, CH_2); ^{13}C (300 MHz, $CDCl_3$, APT) δ 175.4 (CO), 173.9 (CO), 140.4 (C), 131.5 (C), 134.0 (CH), 130.7 (CH), 130.4 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 126.0 (CH), 121.9 (CH), 75.9 (CH), 63.2 (CH), 60.0 (CH), 59.2 (CH), 59.0 (CH), 77.5 ($\mathbf{CH_2}OCH_3$), 49.4 (CH_2), 24.6 (CH_2), 21.0 (CH_2), 38.2 (OCH_3); MS (ES) *m/z* 470 $(M+Na)^+$; HRMS (ES) *m/e* calcd for $C_{26}H_{29}N_3O_4Na$ $(M+Na)^+$ 470.2056, found 470.2047.

(1R,4R,6S,10R)-5-[(S)-(-)-1-amino-2-(1-methoxy-1-methylethyl) pyrrolidine]-4-hydroxybenzyl-8-phenyl-5,8-diazabicyclo [4.3.0] nonane-2-ene-7,9-dione (67b).



To a solution of diene **66b** (0.942 g, 2.920 mmol, 1 equiv) in toluene (5 mL) was added benzaldehyde (0.297 mL, 2.920 mmol, 1 equiv) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. *N*-phenylmaleimide (1.010 g, 5.840 mmol, 2 equiv) was added to the above solution and heated at 80 °C for 3 days, then diluted with EtOAc and stirred at rt for 30 minutes with a saturated solution of sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted three times with EtOAc (25 mL each). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **67b** as a crude product. Purification by flash column chromatography using 1% MeOH in dichloromethane led to the isolation of the pure alcohol **67b** (0.583 g, 42% yield) as pale yellow solid; mp 80-82 ^{0}C. Spectroscopic data for **67b**: IR ($CHCl_3$ cast) 3853,

2932, 1715, 1651, 1597, 1499, 1455, 1382, 1179, 1142, 753, 692, 667, 621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.01 (ddd, J = 1.6, 3.7, 10.6 Hz, 1H, H^3), 5.70 (ddd, J = 2.3, 4.5, 10.6 Hz, 1H, H^2), 4.80 (d, J = 8.5 Hz, 1H, H^6), 4.01 (d, J = 9.6 Hz, 1H, C^{10}), 3.62 (m, 2H, H^1, H^4), 3.21-3.42 (m, 4H, OCH_3, CHN), 2.61-2.78 (m, 2H, CH_2N), 1.51-1.90 (m, 4H, CH_2), 1.12 (s, 6H, CH_3); ^{13}C (300 MHz, $CDCl_3$, APT) δ 175.2 (CO), 174.1 (CO), 140.7 (C), 140.6 (C), 78.5 (C), 130.8 (CH), 129.3 (CH), 129.1 (CH), 128.4 (CH), 128.0 (CH), 127.1 (CH), 126.3 (CH), 122.1 (CH), 76.1 (CH), 67.9 (CH), 63.2 (CH), 60.1 (CH), 49.1 (CH), 50.7 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 38.4 (CH_3), 21.9 (CH_3), 20.6 (CH_3); MS (ES) *m/z* 498 $(M+Na)^+$; HRMS (ES) *m/e* calcd for $C_{28}H_{33}N_3O_4Na$ $(M+Na)^+$ 498.2369, found 498.2372; $[\alpha]^{25}_D$ = -48.9 (*c* 0.50, $CDCl_3$).

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Chapter Two

N,N-Diethanolaminomethyl Polystyrene: An Efficient Solid Support to Immobilize Boronic Acids.

I. INTRODUCTION

Combinatorial chemistry is becoming an increasingly important tool in drug discovery. Solid-phase organic synthesis (SPOS) is particularly suitable for combinatorial library synthesis. One of the goals of SPOS is to synthesize diverse sets of resin-bound small, non-peptidic, drug-like molecules in good yields and purity. This goal in turn created a need for new types of resins and linkers with different physical and chemical properties to accommodate a wide range of substrates and reactions. The advantage of SPOS is the ease with which reaction work-up and purification can be conducted. It allows the use of excess of reagents to drive reactions to completion. It also allows the separation of reagents, starting materials and solvents from the desired resin bound product by simple filtration.

Several boron derivatives have been known to play a significant role in a variety of biological process.[1] They also have great medicinal potential in boron neutron capture therapy. Boronic acids are not easy to isolate because of their sensitivity to air oxidation and their amphiphilic properties. Diethanolamine boronate adducts have been used to stabilize boronic acids by coordination of the nitrogen to the boron.

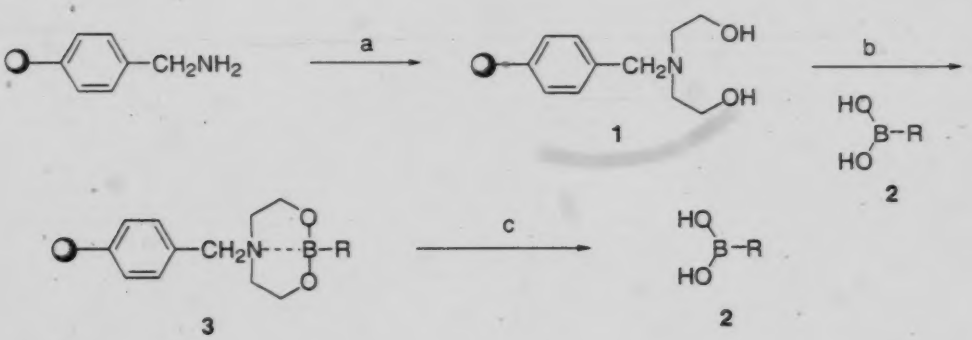
II. RESULTS AND DISCUSSION

We envisioned that a diethanolamine-based linking strategy, could give access to the immobilization a wide variety of boronic acids and esters. Herein, we report the preparation of *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS), the first resin capable of immobilizing boronic acids. The DEAM-PS resin can immobilize aryl, alkenyl and alkyl boronic acids quantitatively in a wide range of organic solvents.

A. Preparation of DEAM-PS resin 1.

The DEAM-PS resin **1** has been synthesized using aminomethylated polystyrene (AM-PS) with excess ethylene oxide at 50 °C in a THF/water solvent mixture in a sealed, pressure-resistant tube (Scheme 2.1). The current shortage of reliable and non-destructive analytical techniques for monitoring on-resin reactions is often rate limiting in the development of the new solid phase chemistry. However, we have been able to successfully employ two simple tests to prove complete dialkylation of AM-PS to give DEAM-PS resin (**1**). First, the resulting resin **1** gave a negative result with a

Kaiser's ninhydrin assay and second, a basic tertiary amine site was confirmed by a positive reaction with bromophenol blue.



Scheme 2.1. Synthesis of DEAM-PS resin **1**. Immobilization and subsequent release of boronic acid **2**. a) Ethylene oxide (excess), THF/H_2O 9/1 (sealed tube), 50 °C, 24 h. b) boronic acid **2**, solvent, rt, 15 min. c) THF/H_2O/AcOH 90/5/5, rt, 1 h; or THF/H_2O 9/1, rt, 2h.

B. Reaction parameters.

We next examined the reaction parameters (i.e. solvent and time) for the optimal attachment of boronic acids and cleavage conditions. As shown in Table 2.1, a broad range of organic solvents was screened against *p*-tolylboronic acid (**2a**). We found that this method works well with almost all solvents. The best solvent obtained for the cleavage was a THF:water:acetic acid (90:5:5)

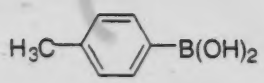
mixture. In the case of acid-sensitive boronic acids, the resin can be cleaved under neutral conditions with prolonged exposure to THF:water (9:1). My colleague Michel Gravel did this work. Upon implementation of this protocol, this resin was found to be quite effective. Simple agitation at room temperature for 15 minutes with various boronic acids produced the highly pure products in good yields after cleavage. As shown in Table 2.1, the percentage yields were determined from the amounts of boronic acids recovered after subsequent hydrolytic release from the support based on the loading of the DEAM-PS resin.

The efficiency with which resin **1** can be used to immobilize boronic acids was tested in the following control experiment. A slight excess of resin **1** was treated with a solution of *p*-tolyboronic acid in anhydrous THF to give the polymer supported boronic ester. After careful washing with THF and cleavage, the boronic acid was recovered in high yield.

C. Substrate generality.

To demonstrate the generality of this procedure, a variety of boronic acids were immobilized on the DEAM-PS resin. The results

are listed in Table 2.1. A wide range of electron-rich and arylboronic acids can couple quantitatively with resin **1** in dry THF after a few minutes. It can also couple efficiently with an alkenylboronic acid (entry 13) and even with an air-sensitive alkylboronic acid (entry 14), although with a lower yield in this case. The efficiency of resin **1** to immobilize boronic acids was compared with glycerol-PS resin. The use of glycerol-PS resin leads to less then 50% coupling under the same reaction conditions. This result indicates the increased stability of the boronate linker through nitrogen coordination.



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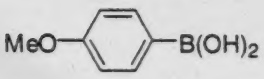

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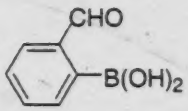

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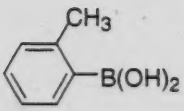

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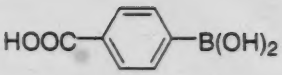

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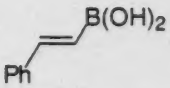

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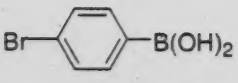

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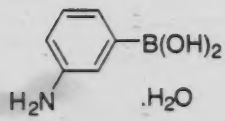

2f

2i

Table 2.1. Coupling of different boronic acids 2 with DEAM-PS resin 1.

Entry	Boronic acid	Solvent	Yield [%][a]	Purity [%][b]
1	**2a**	CH_2Cl_2	>95	>95
2	**2a**	DMF	87	>95
3	**2a**	Toluene	>95	>95
4	**2a**	CH_3OH	53	>95
5	**2a**	Et_2O	90	>95
6	**2a**	THF	>95	>95
7	**2b**	THF	>95	>95
8	**2c**	THF	>95	>95
9	**2d**	THF	>95	>95
10	**2e**	THF	>95	>95
11	**2f**	THF	>95	>90
12	**2g**	THF	90	>95
13	**2h**	THF	91	>90
14	**2i**	THF	50	>90

[a] Based on the amount of boronic acid recovered after cleavage of the resin for 1 h in a THF/H_2O/AcOH mixture (90/5/5). [b] Estimated

through comparison of the ^{1}H NMR spectra of the recovered boronic acids and the starting material.

III. CONCLUSION

In summary, a mild and efficient procedure for the preparation of DEAM-PS resin (**1**) is described, and its synthetic utility is illustrated by isolating unstable boronic acids from reaction mixtures.[2] The mild cleavage conditions (THF:H_2O) are well suited for acid-sensitive boronic acids. Other transformations of boronic acid derivatives on solid support were also demonstrated.[2] DEAM-PS resin is also useful in resin-to-resin Suzuki coupling.[3] This allows access to unsymmetrically functionalized biphenyl compounds. Further investigations on the scope of resin **1** are underway in the Hall laboratory.

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University of Alberta Department of Chemistry
X-Ray Crystallography Laboratory

STRUCTURE REPORT

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Date: 18 February 2000
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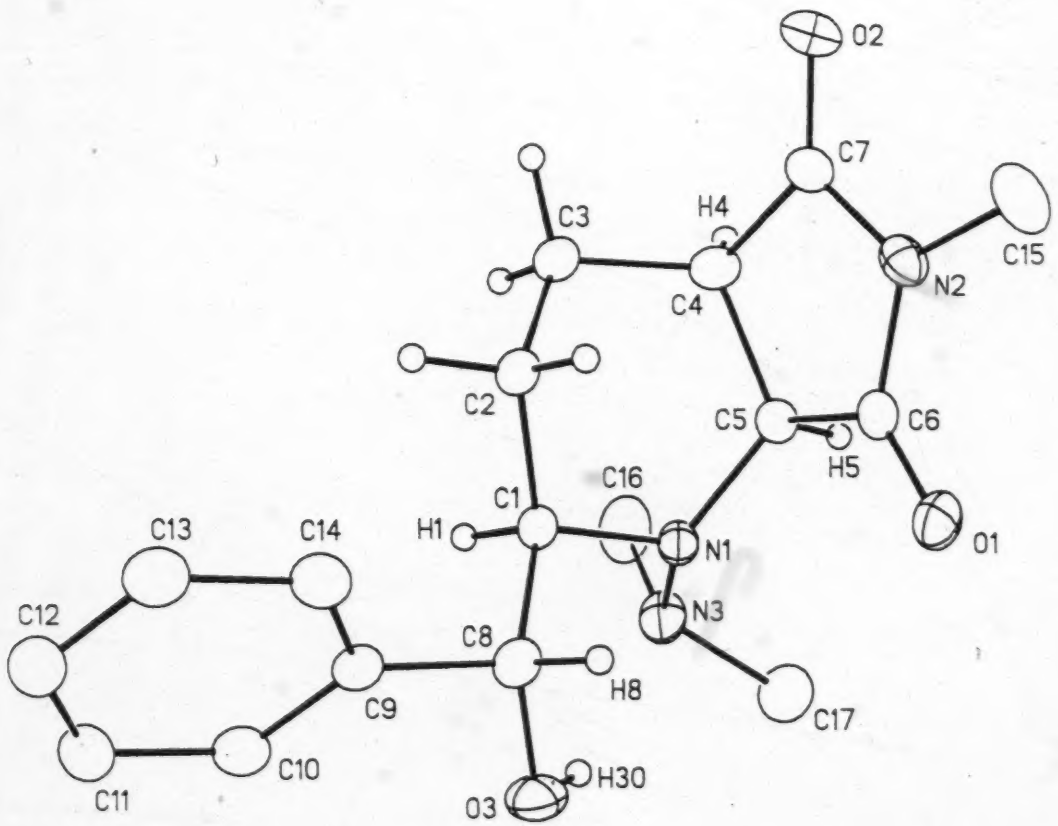
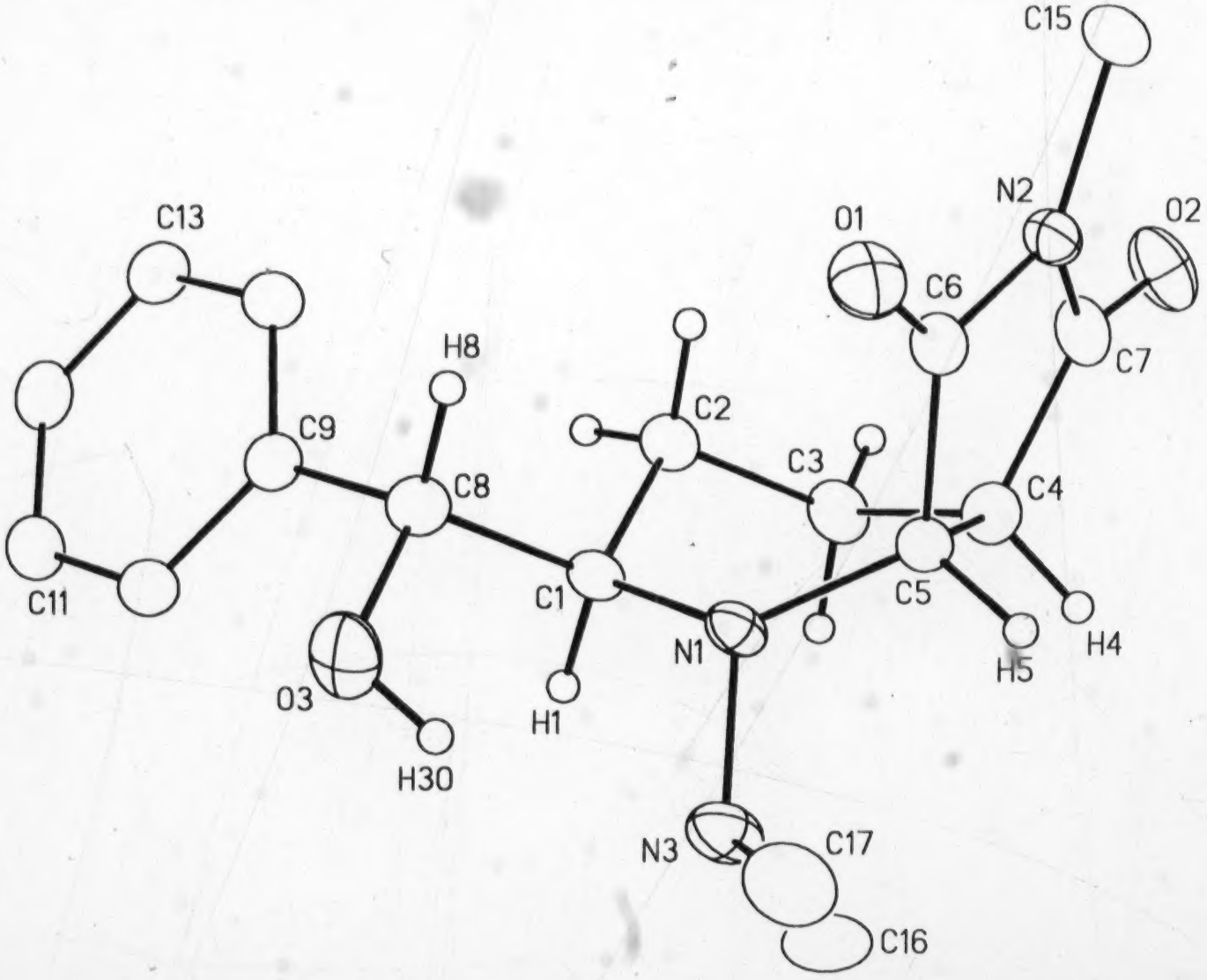
Formula: $C_{17}H_{23}N_3O_3$
Supervisor: D. G. Hall

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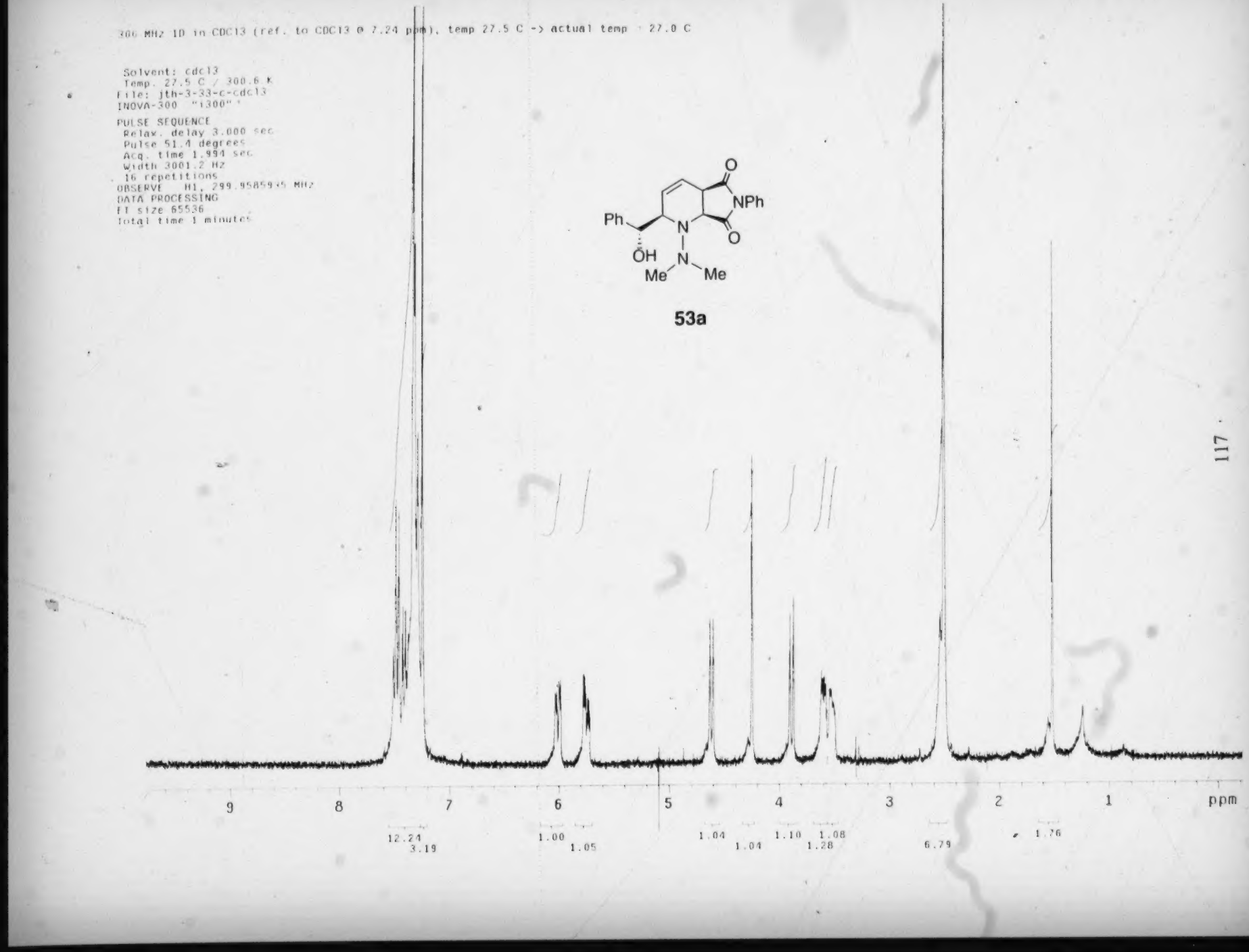
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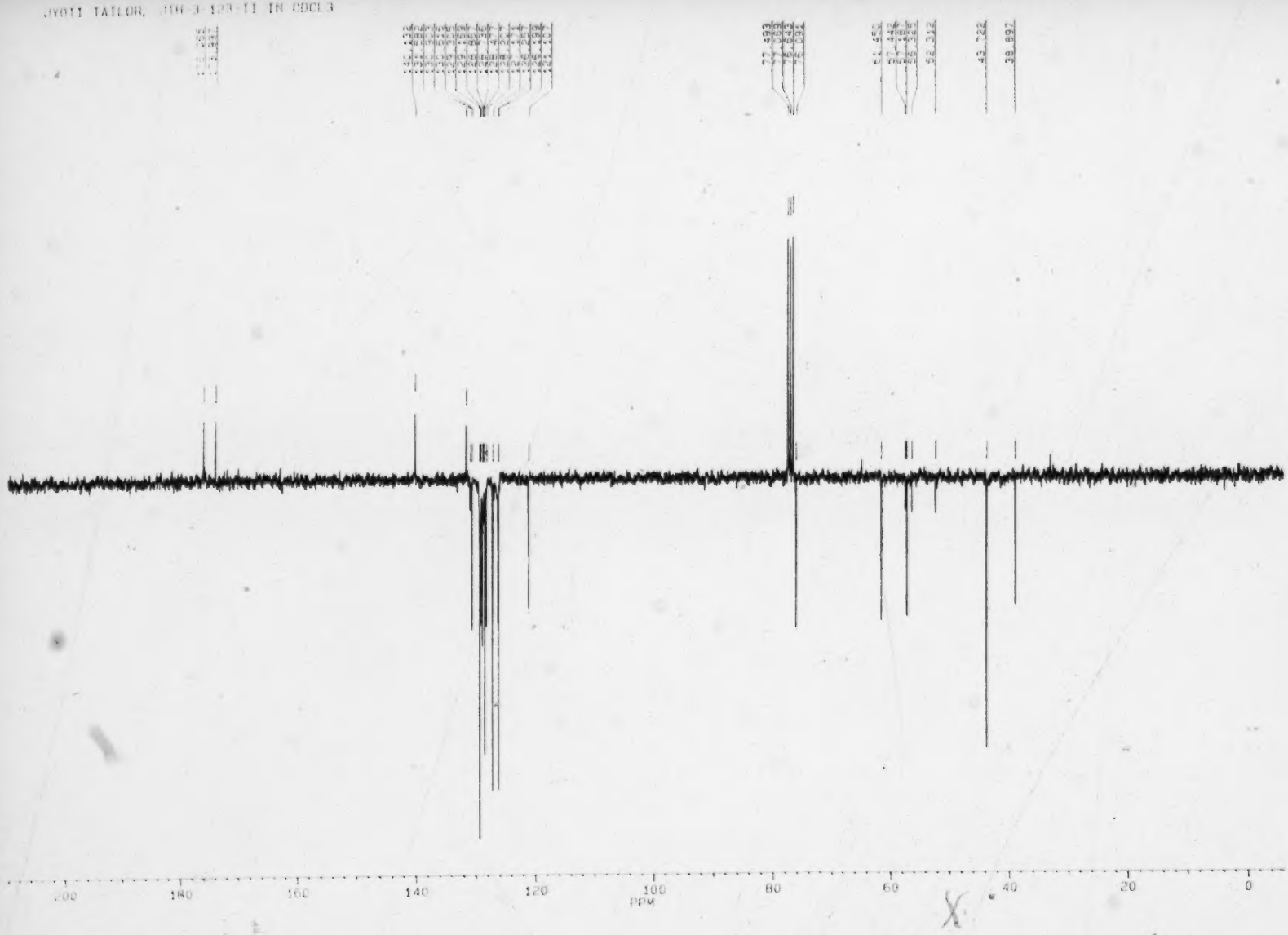
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118

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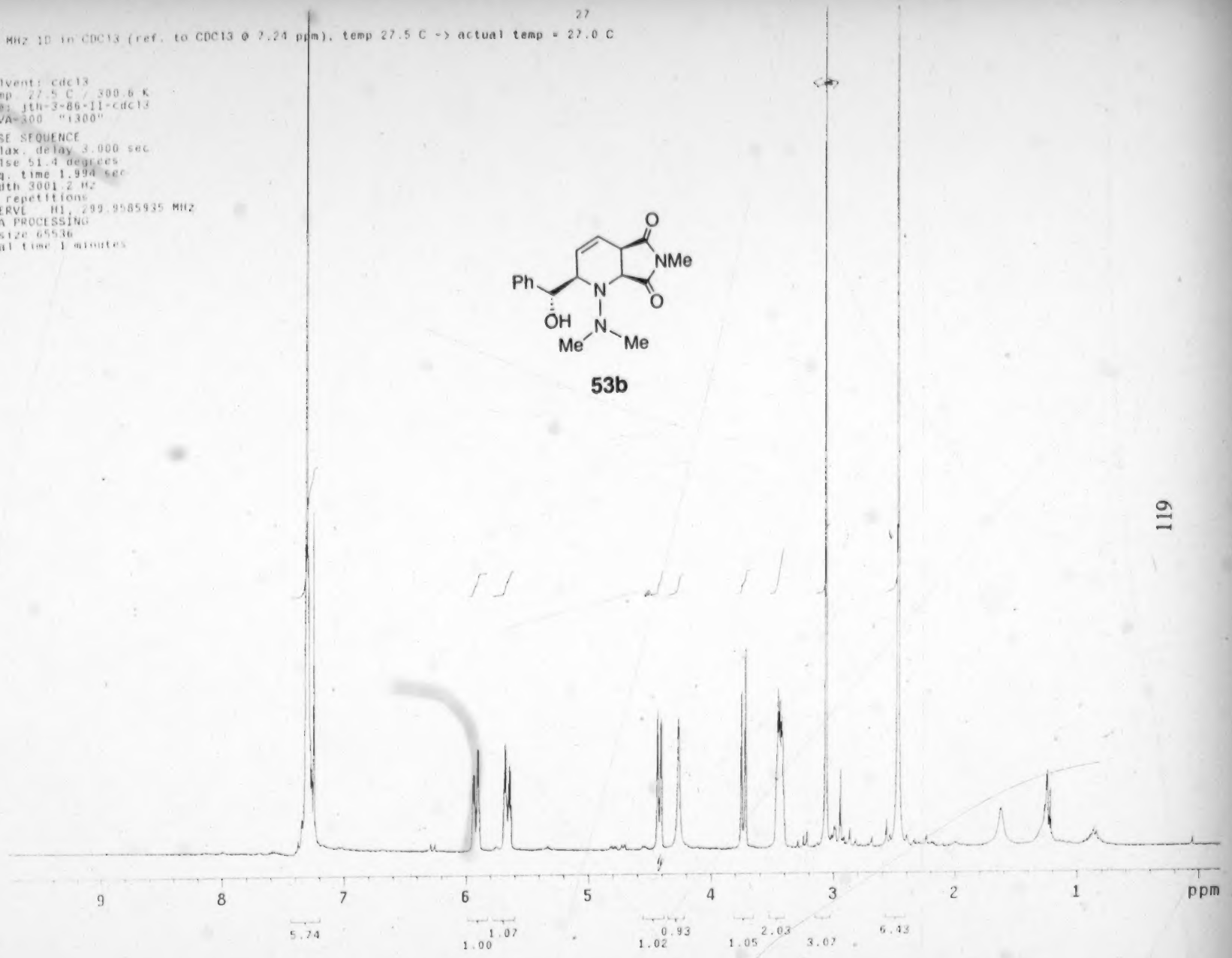

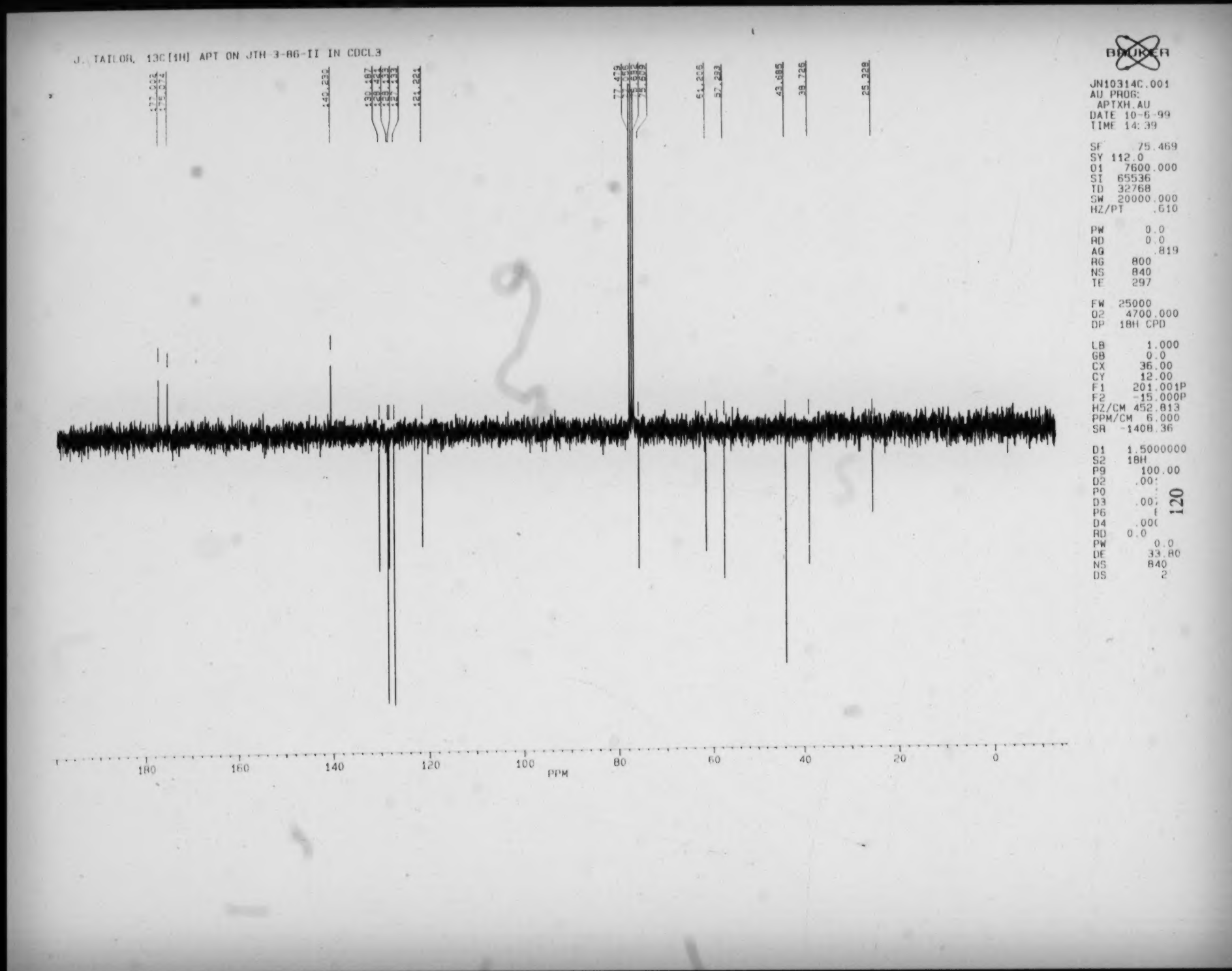
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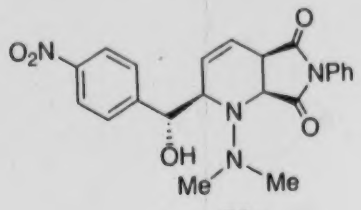

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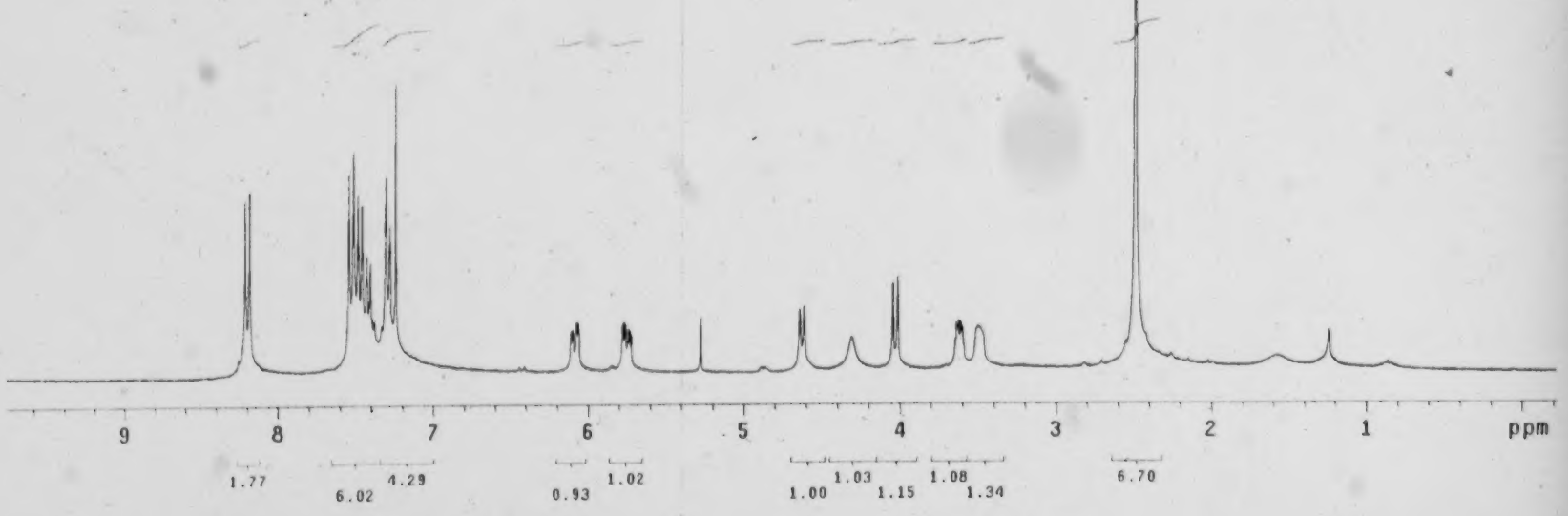

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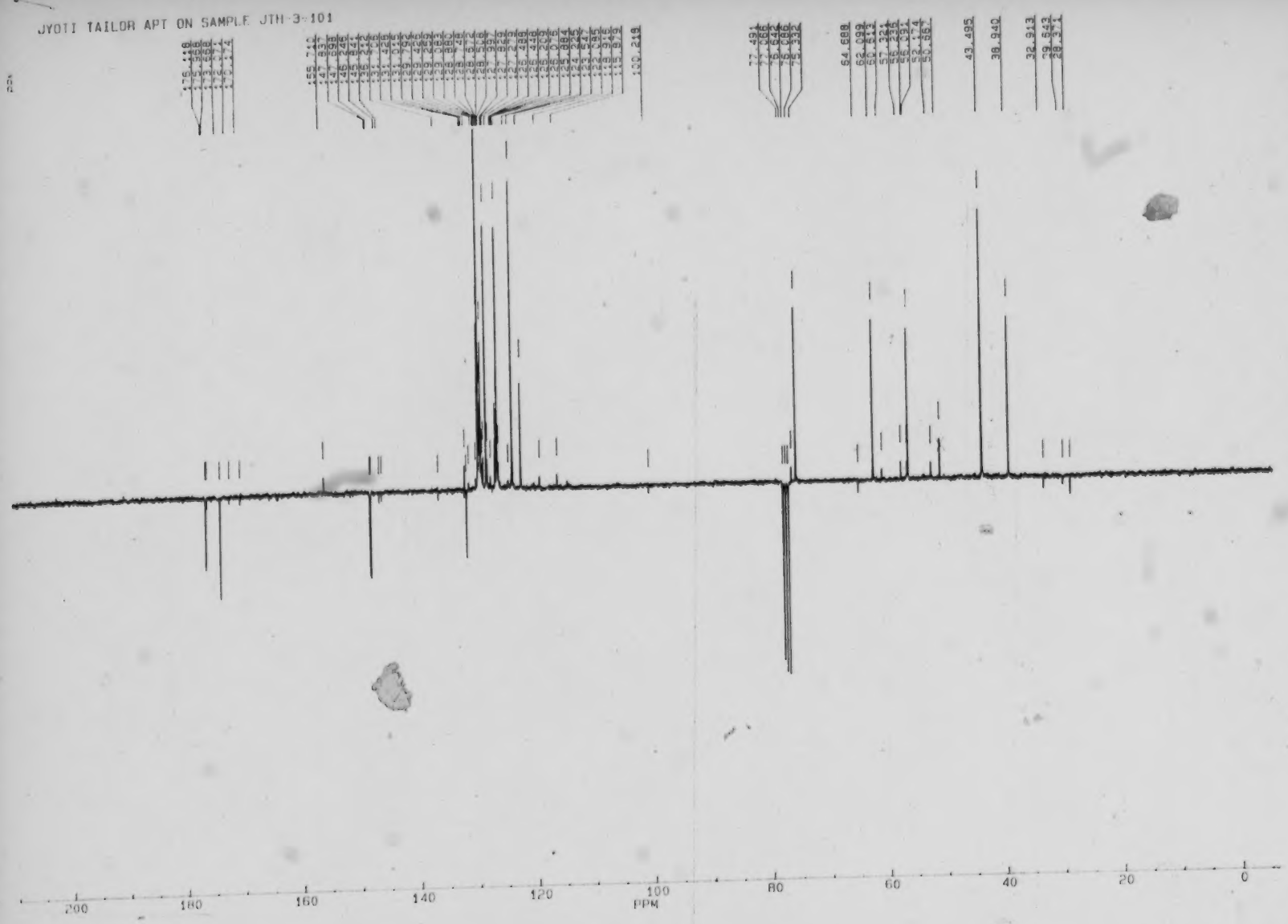

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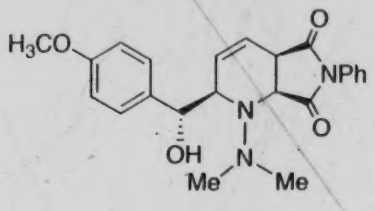

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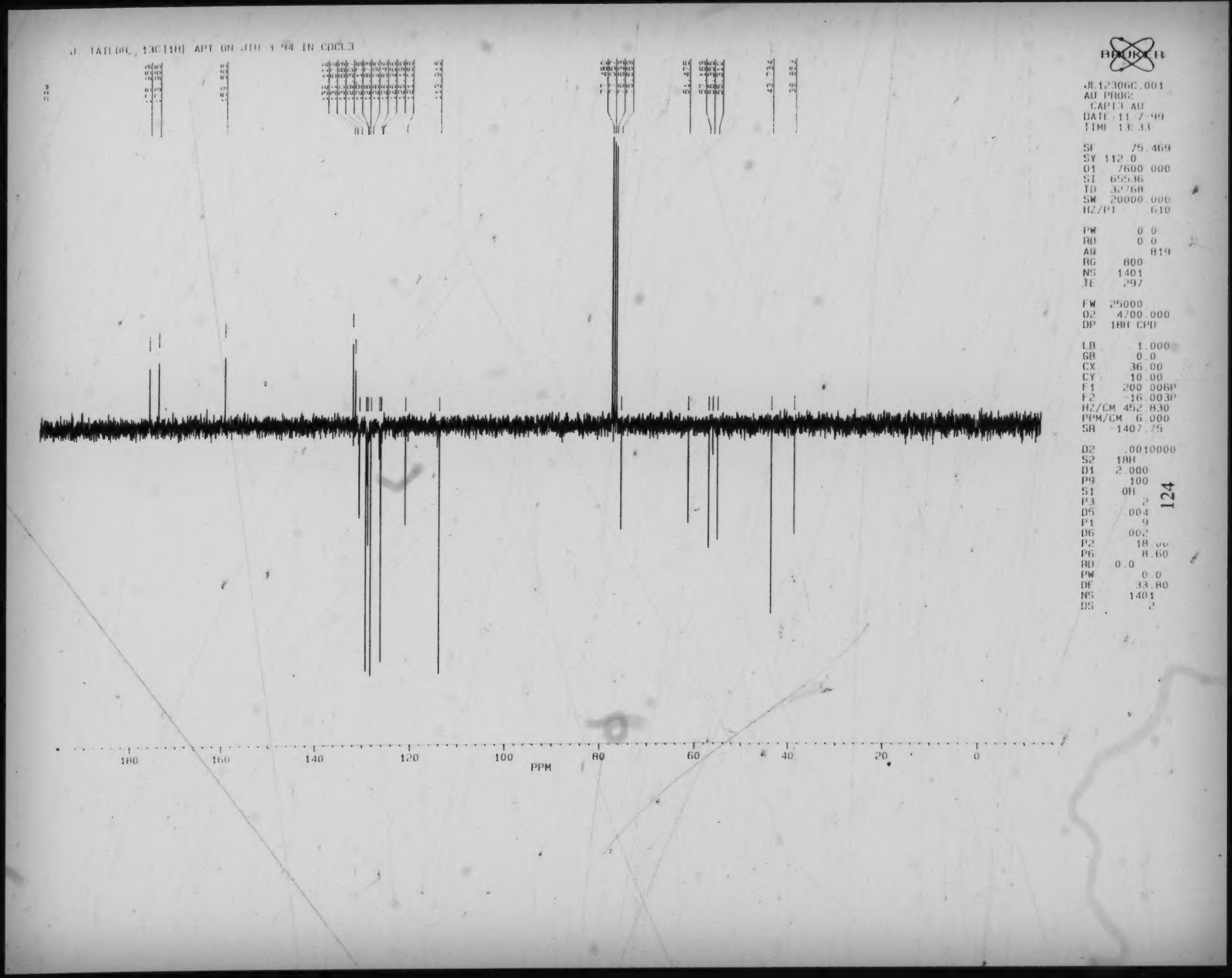
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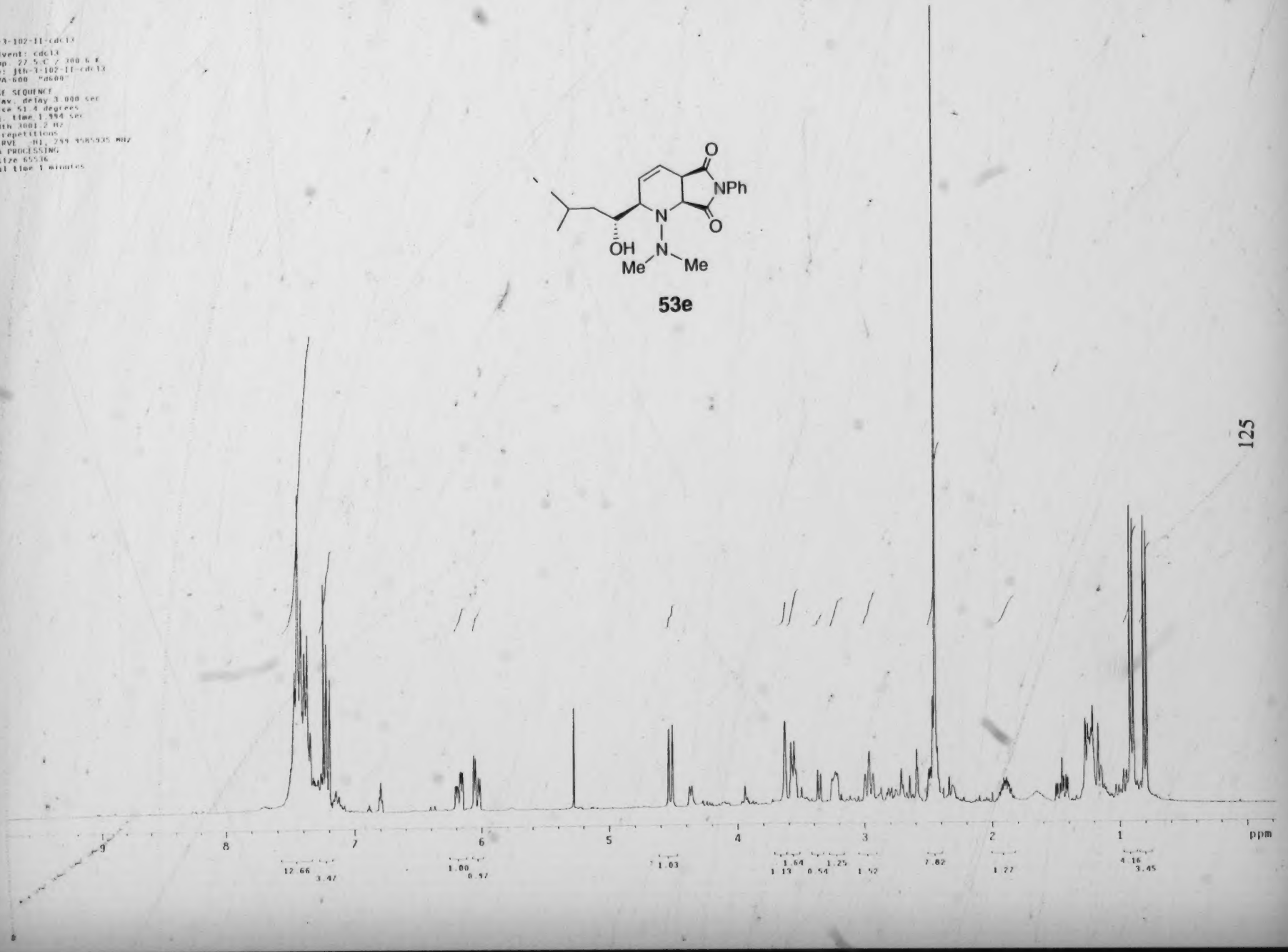
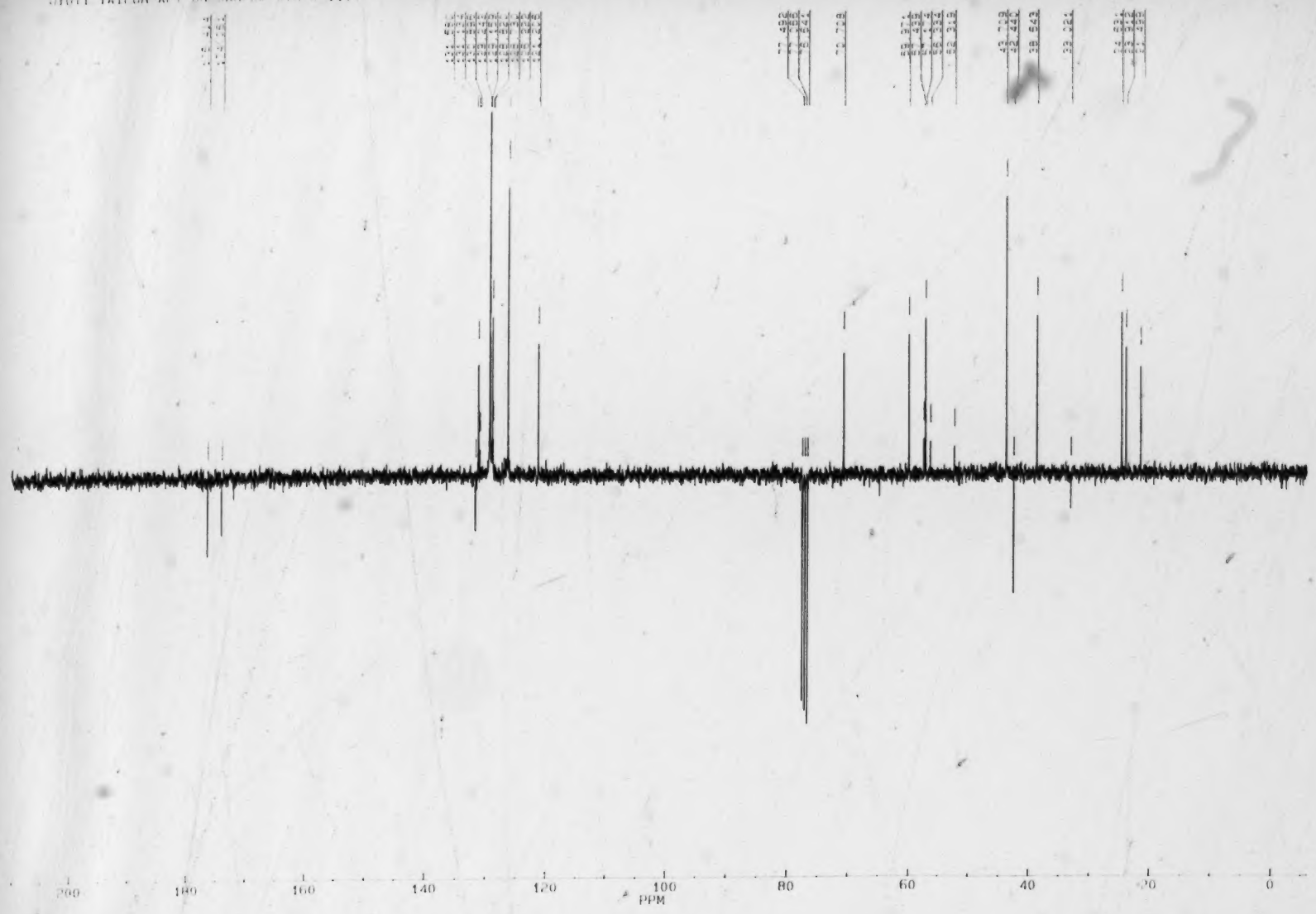
53e

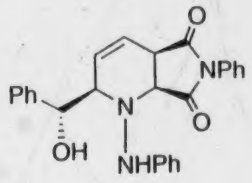



JYOTI TAILOR API DE SAMPLE JTH-3-111
200
180
160
140
120
100
80
60
40
20
0
PPM

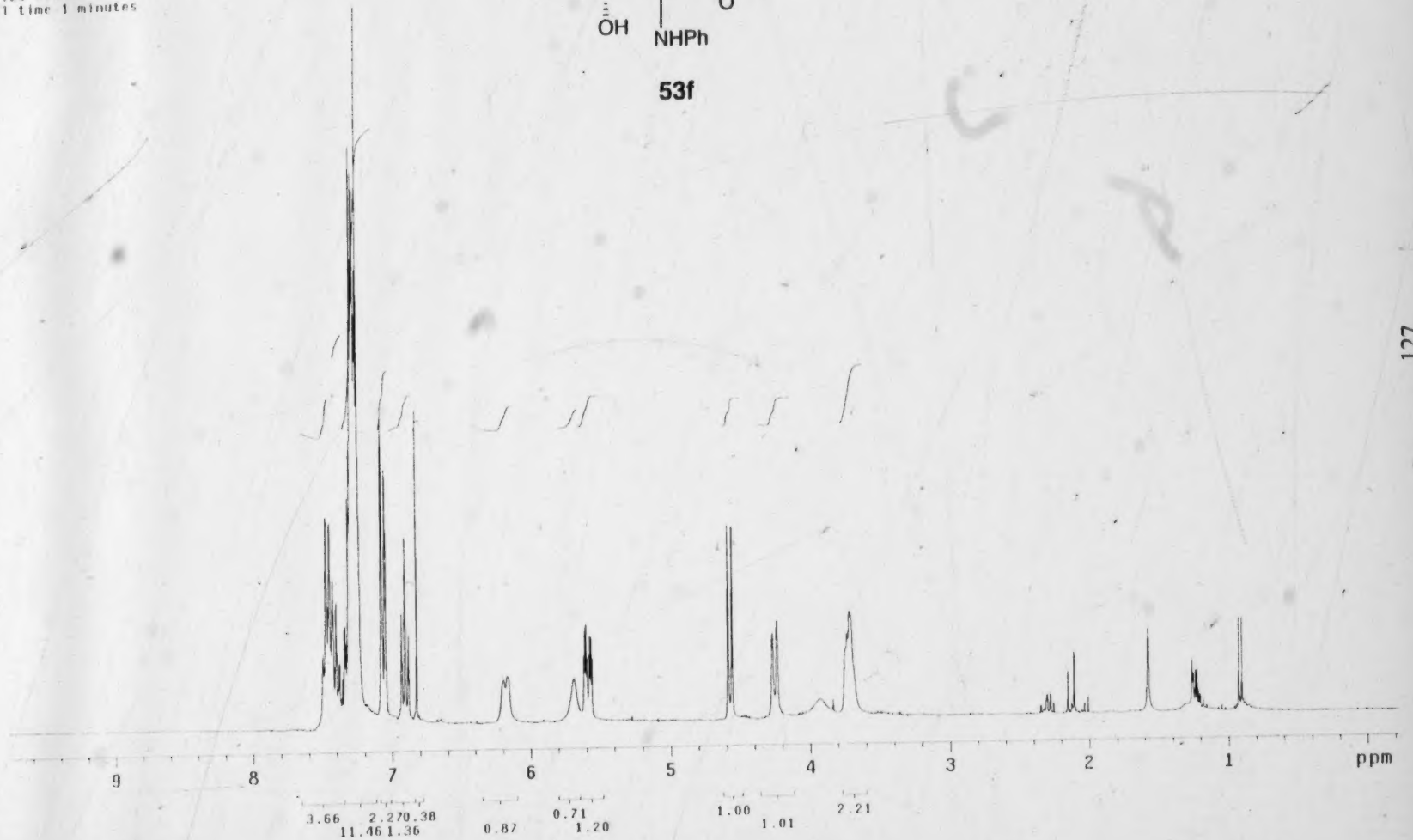
jth-3-139-II-cdcl3

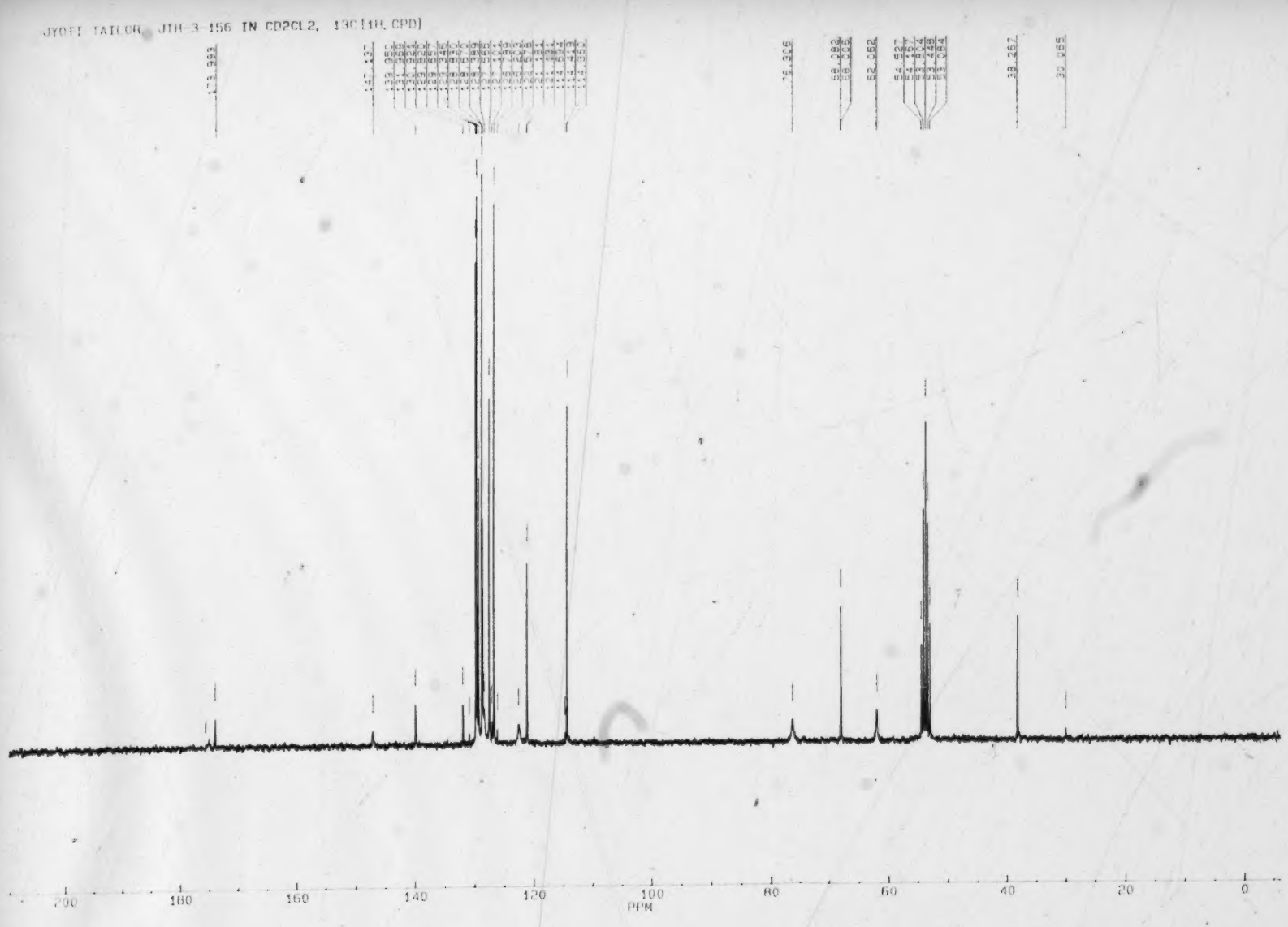
Solvent: cdcl3
Temp. 27.5 C / 300.6 K
File: jth-3-139-II-cdcl3
INOVA-300 "1300"

PULSE SEQUENCE
Relax. delay 3.000 sec
Pulse 51.4 degrees
Acq. time 1.994 sec
Width 3001.2 Hz
16 repetitions
OBSERVE H1, 299.9585935 MHz
DATA PROCESSING
FT size 65536
Total time 1 minutes



53f





BRUKER

SE170F 102
AU PROG
X02.AU
DATE 2 10 99
TIME 5:41

SF 75.469
SY 112.0
O1 19000.000
SI 32768
TD 32768
SW 22727.273
HZ/PT 1.387

PW 0.0
RD 0.0
AQ .721
RG 800
NS 12000
TE 297

FW 28500
O2 5200.000
DP 1BH CPD

LB 1.200
GB .010
CX 36.00
CY 16.00
F1 210.017P
F2 -5.974P
HZ/CM 452.793
PPM/CM 6.000
SR 710.18

DS .1000000
P9 1C
S1 1BH
P0
RGA
RD 0.0
PW
DE 30.00
NS 12000
DS 0
D1 .1000000

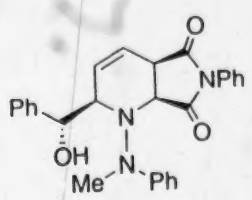
128

jth-3-195-cdcl3

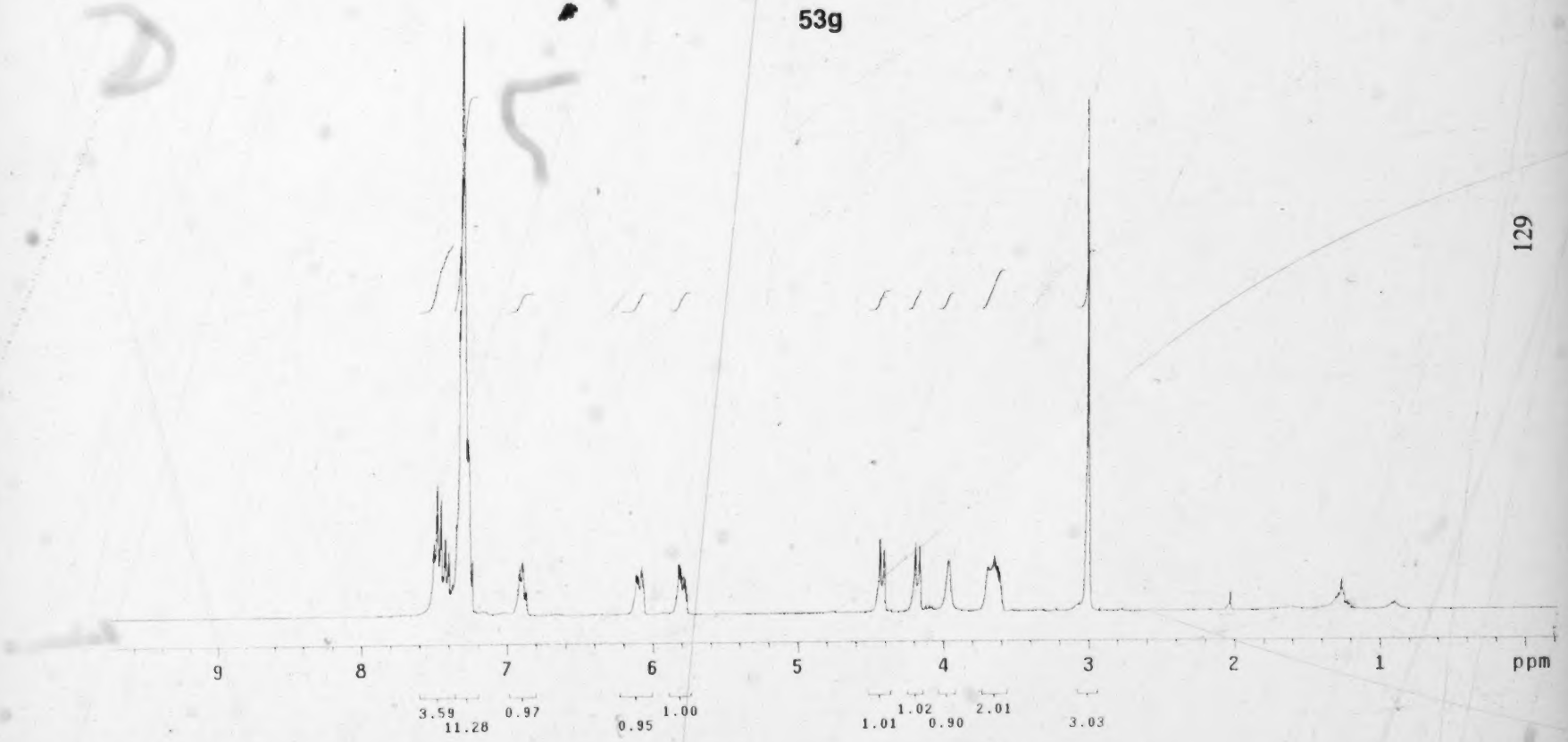
Pulse Sequence: s2pul

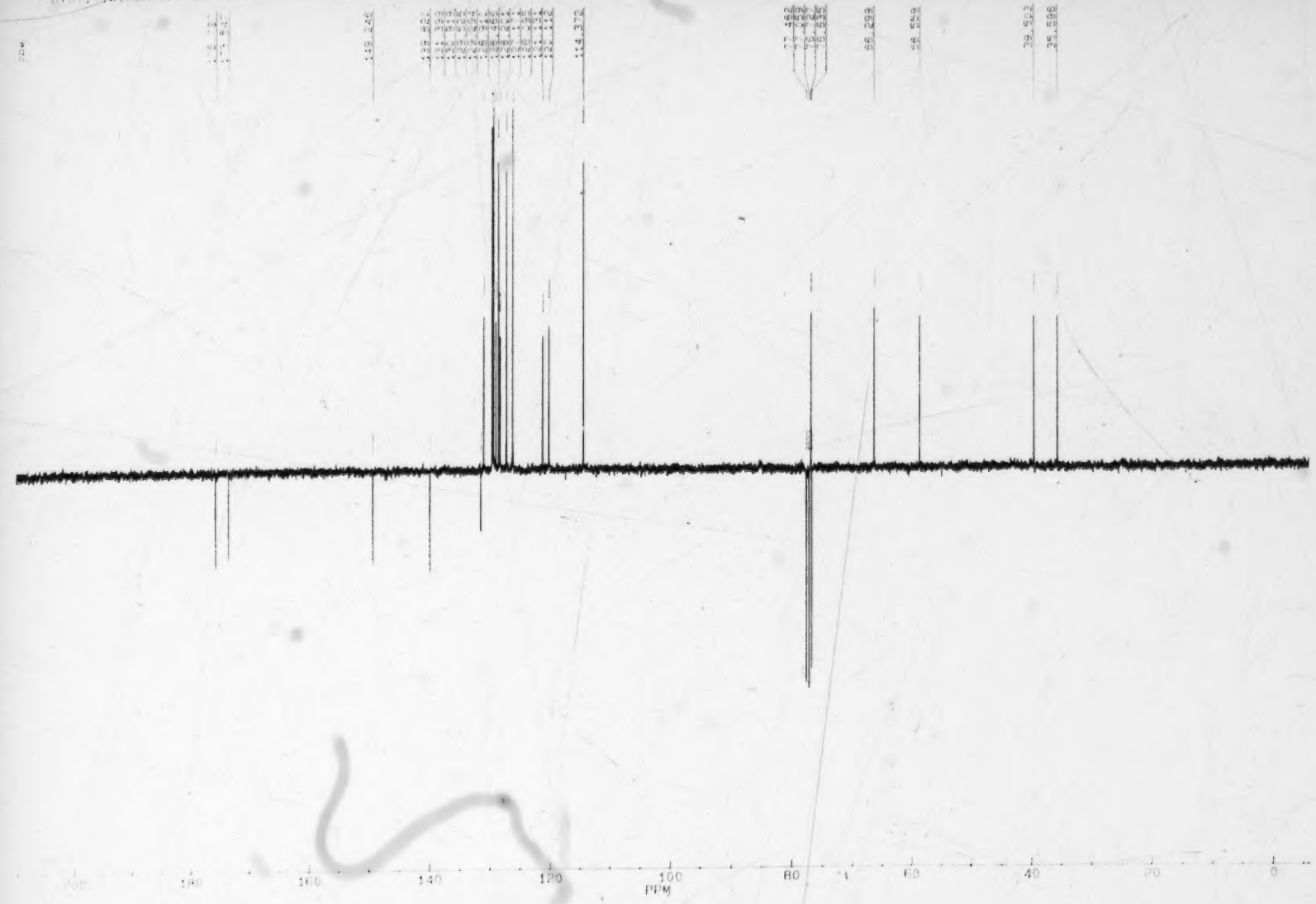
Solvent: cdcl3
Temp. 27.5 C / 300.6 K
File: jth-3-195-cdcl3
INOVA-300 "i300"

PULSE SEQUENCE
Relax. delay 3.000 sec
Pulse 51.4 degrees
Acq. time 1.991 sec
Width 3001.2 Hz
16 repetitions
OBSERVE H1, 299.9585935 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 30 sec



53g





BRUKER

QC213060
AU PROG
APTXH.AU
DATE 10 11 99
TIME 13:00

SF 75.469
SY 112.0
O1 7300.000
SI 65536
TD 32768
SW 21739.130
HZ/PT 663

PW 0.0
RD 0.0
AQ .754
RG 800
NS 1440
TE 297

PW 27200
O2 4800.000
DP 18H SPD

LB 1.000
GB .010
CX 36.00
CY 10.00
F1 210.003P
F2 -5.995P
HZ/CM 452.806
PPM/CM 6.000
SR -1405.49

D1 2.0
S2 18H
PG 1
D2 0
P0
D3 0
PE 8.40
D4 0001000
RD 0.0
PW 0.0
DE 31.30
NS 1440
DS 2

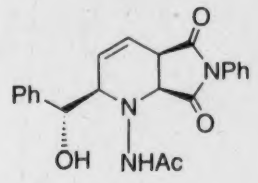
130

jth-3-185-I-cdcl3

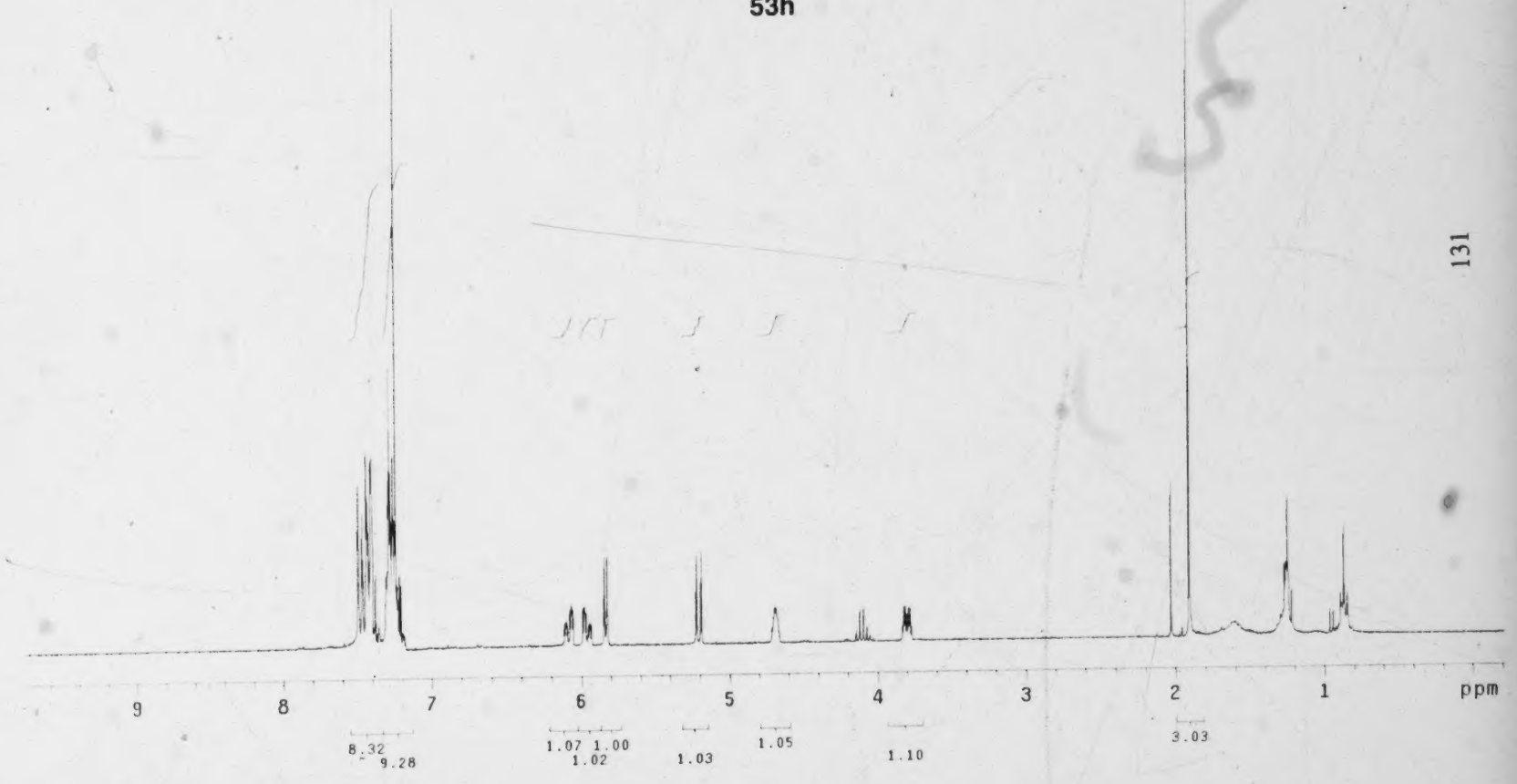
Pulse Sequence: s2pul

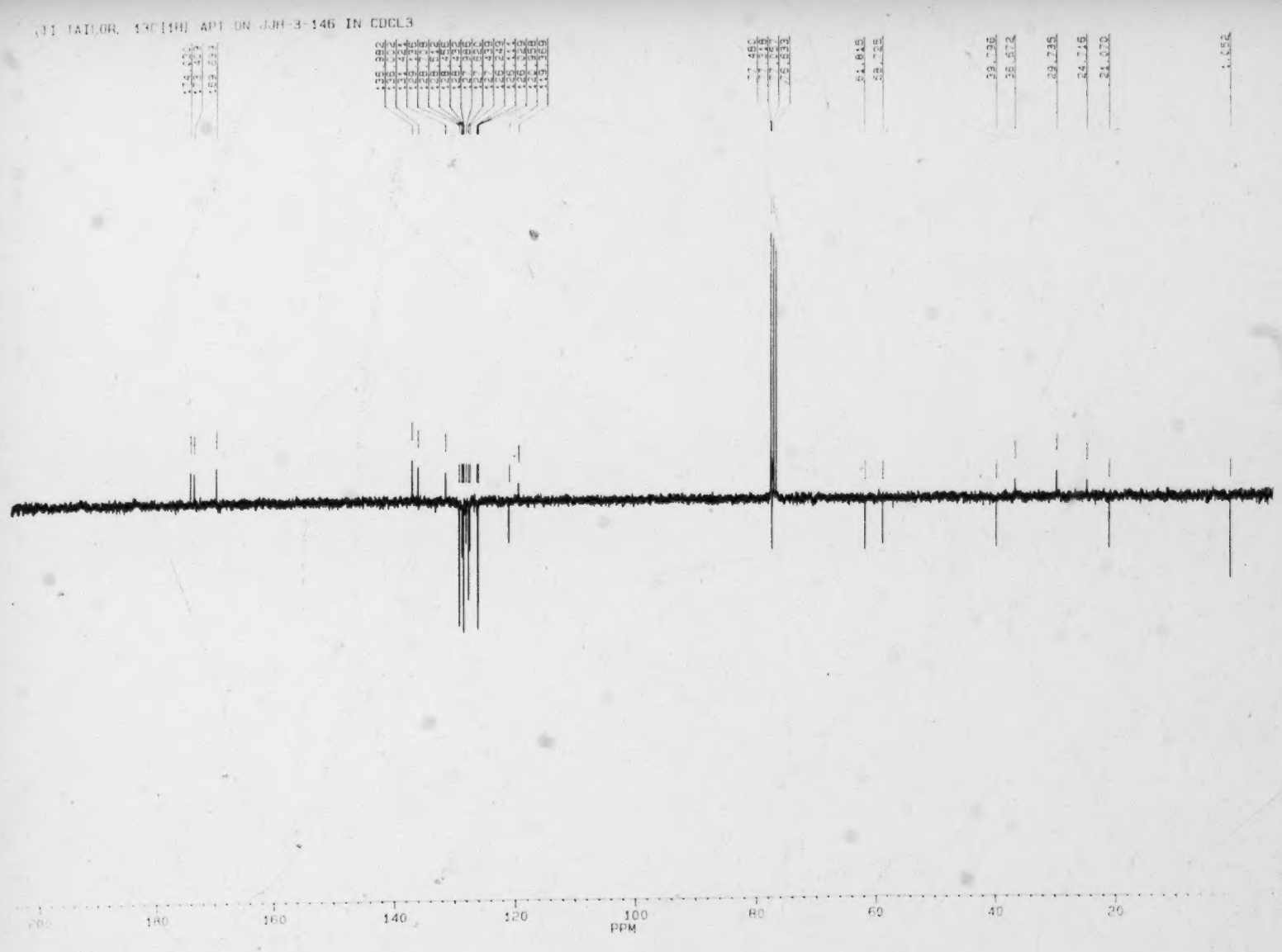
Solvent: cdcl3
Temp. 27.5 C / 300.6 K
File: jth-3-185-I-cdcl3
INOVA-300 "I300"

PULSE SEQUENCE
Relax. delay 3.000 sec
Pulse 51.4 degrees
Acq. time 1.994 sec
Width 3001.2 Hz
16 repetitions
OBSERVE H1, 299.9585935 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 30 sec



53h





BRUKER

AU23309C 001
AU PROG:
CAPT3.AU
DATE 2-10-99
TIME 16:34

SF 75.469
SY 112.0
O1 7600.000
SI 65536
ID 32768
SW 20000.000
HZ/PT .610

PW 0.0
RD 0.0
AQ .819
RG 800
NS 2201
TE 297

FW 25000
O2 4700.000
DP 18H CPD

LB 1.000
GB 0.0
CX 36.00
CY 0.0
F1 210.002P
F2 -6.007P
HZ/CM 452.830
PPM/CM 6.000
SR -1408.36

D2 .0010000
S2 18H
D1 2.00
P9 10
S1 0H
P3
D5 .00
P1
D6 .0020000
P2 18.00
P6 8.60
RD 0.0
PW 0.0
DE 33.80
NS 2201
DS 2

132

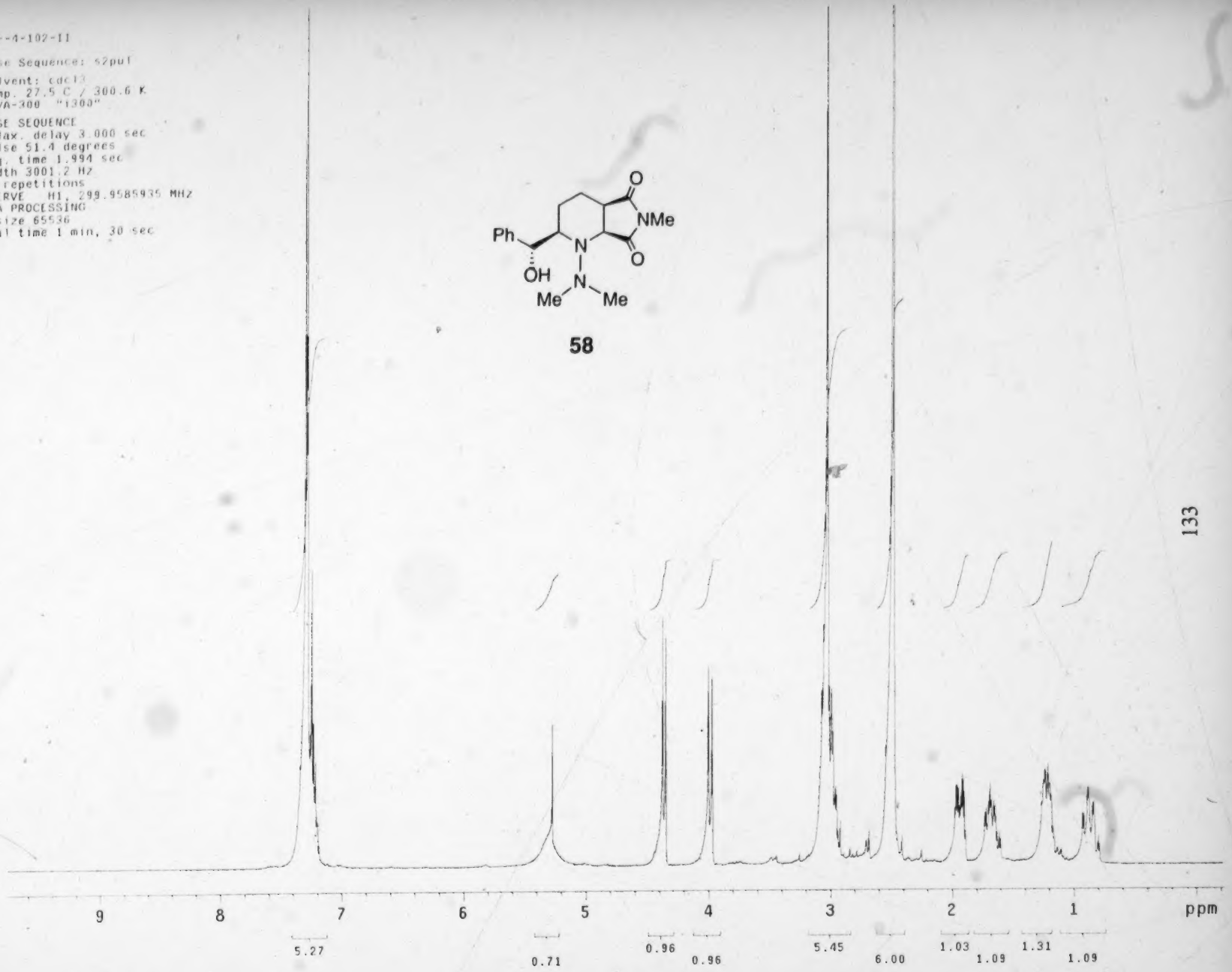
jth--4-102-II

pulse Sequence: s2pul

Solvent: cdcl3
Temp. 27.5 C / 300.6 K
INOVA-300 "i300"

PULSE SEQUENCE
Relax. delay 3.000 sec
Pulse 51.4 degrees
Acq. time 1.994 sec
Width 3001.2 Hz
16 repetitions
OBSERVE H1, 299.9585935 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 30 sec

58



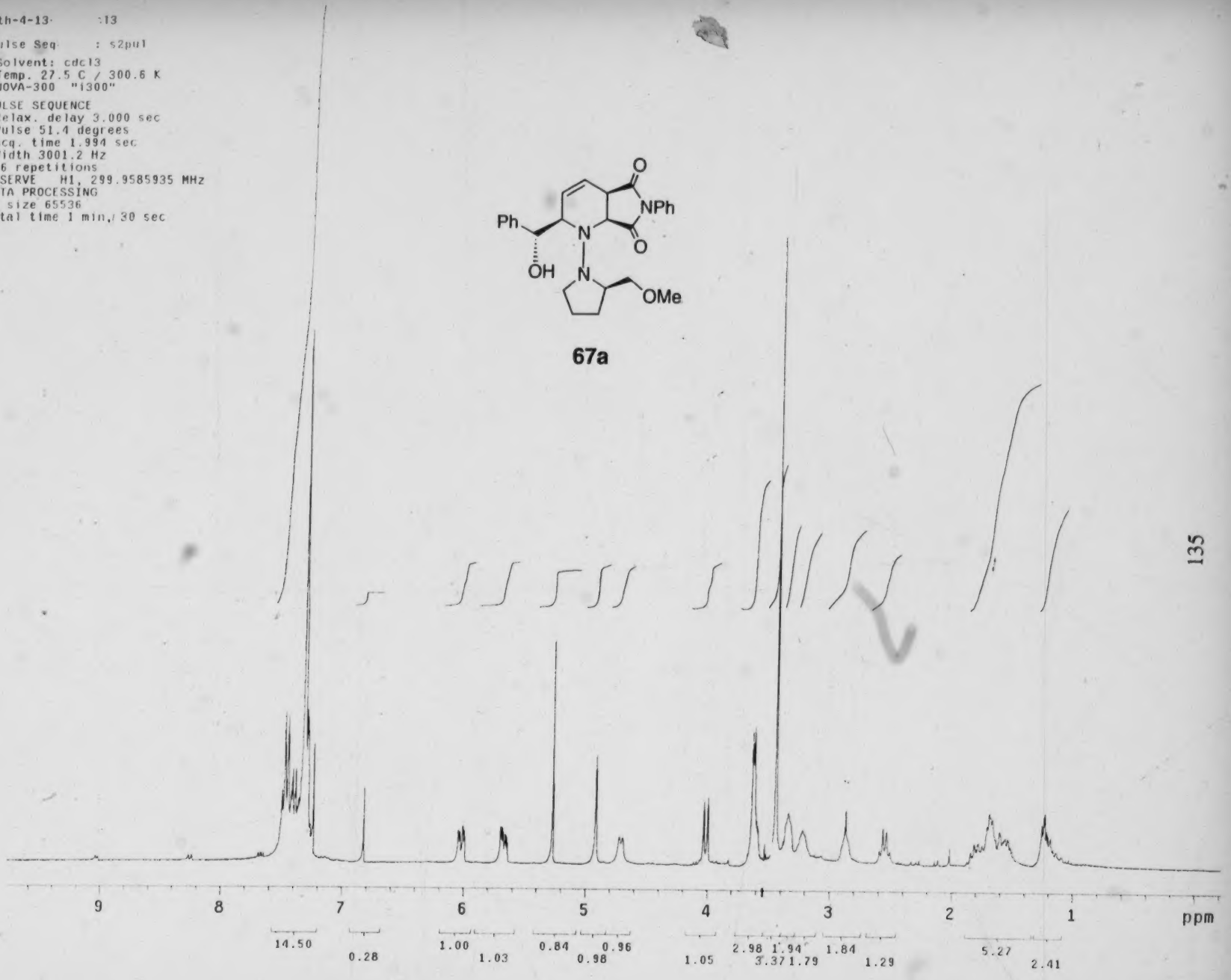
jth-4-13 :13

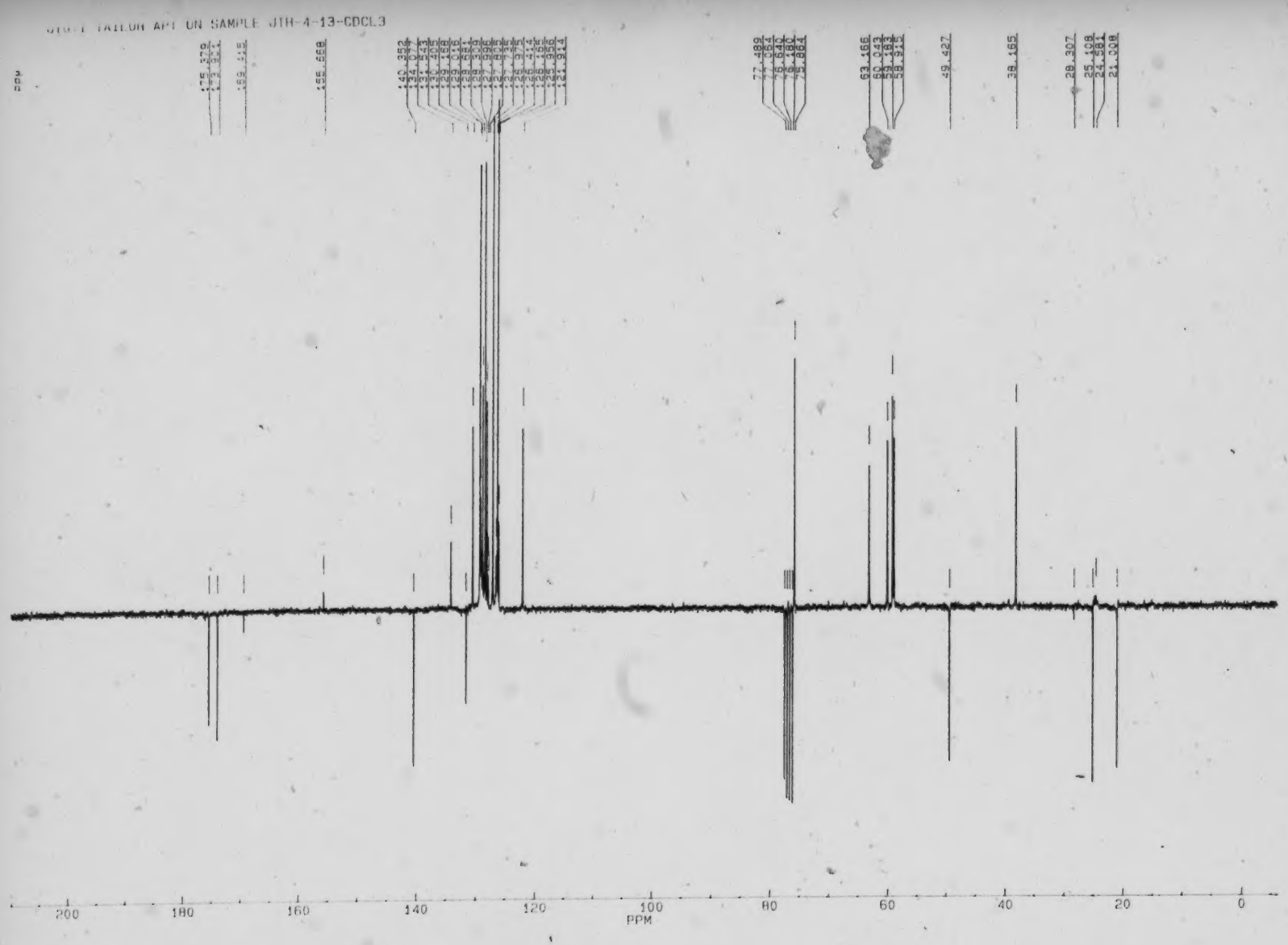
Pulse Seq : s2pul

Solvent: cdcl3
Temp. 27.5 C / 300.6 K
INOVA-300 "i300"

PULSE SEQUENCE
Relax. delay 3.000 sec
Pulse 51.4 degrees
Acq. time 1.994 sec
Width 3001.2 Hz
16 repetitions
OBSERVE H1, 299.9585935 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 30 sec

67a





BRUKER

OC27309C
AU PROG:
APTXH.AU
DATE 6-12-99
TIME 16:18

SF 75.469
SY 112.0
O1 7300.000
SI 32768
TD 32768
SW 21739.130
HZ/PT 1.327

PW 0.0
RD 0.0
AQ .754
RG 800
NS 2095
TE 297

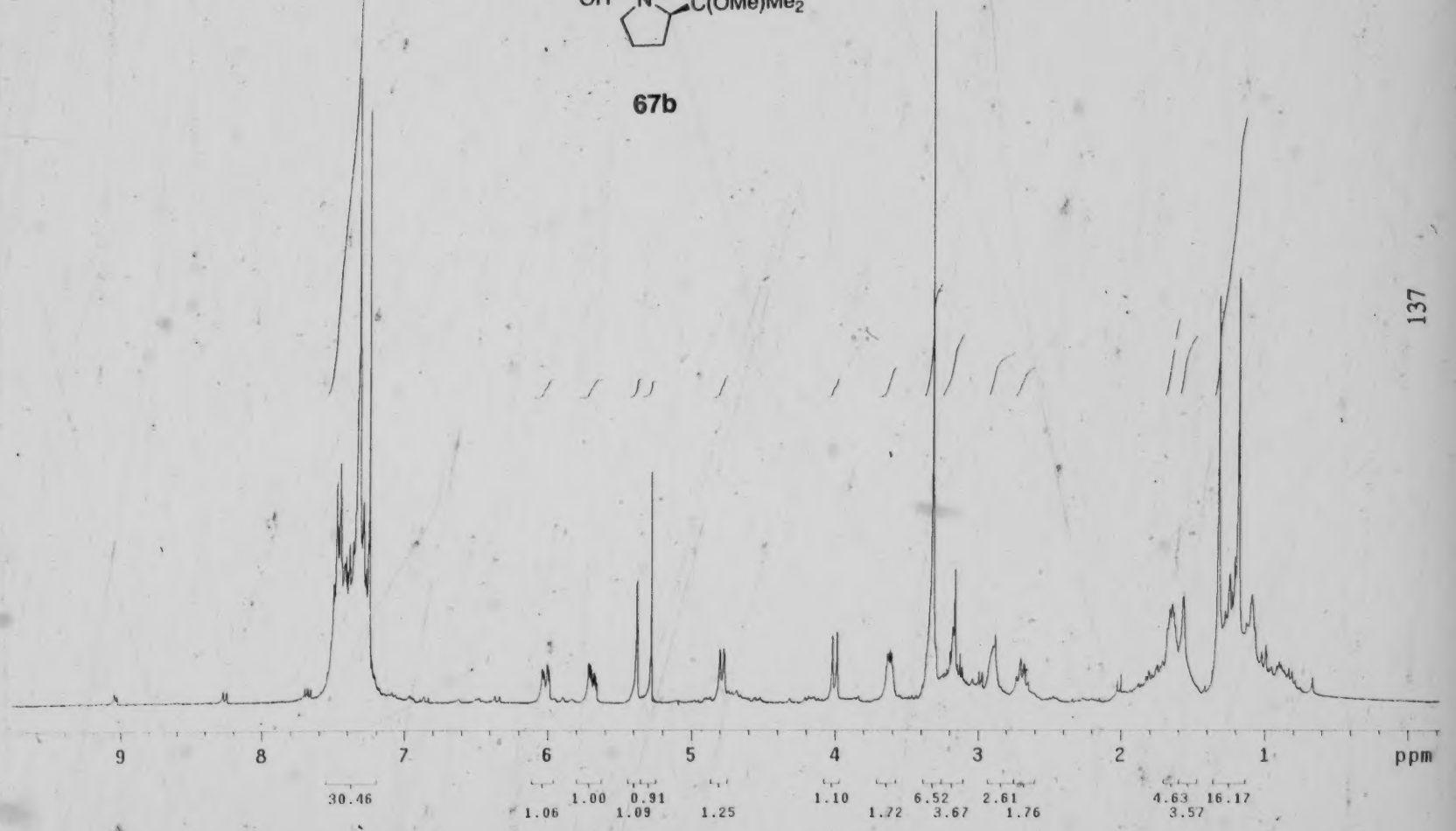
FW 27200
O2 4800.000
DP 1BH CPD

LB 1.200
GB .010
CX 36.00
CY 14.00
F1 210.011P
F2 -5.995P
HZ/CM 452.825
PPM/CM 6.000
SR -1397.53

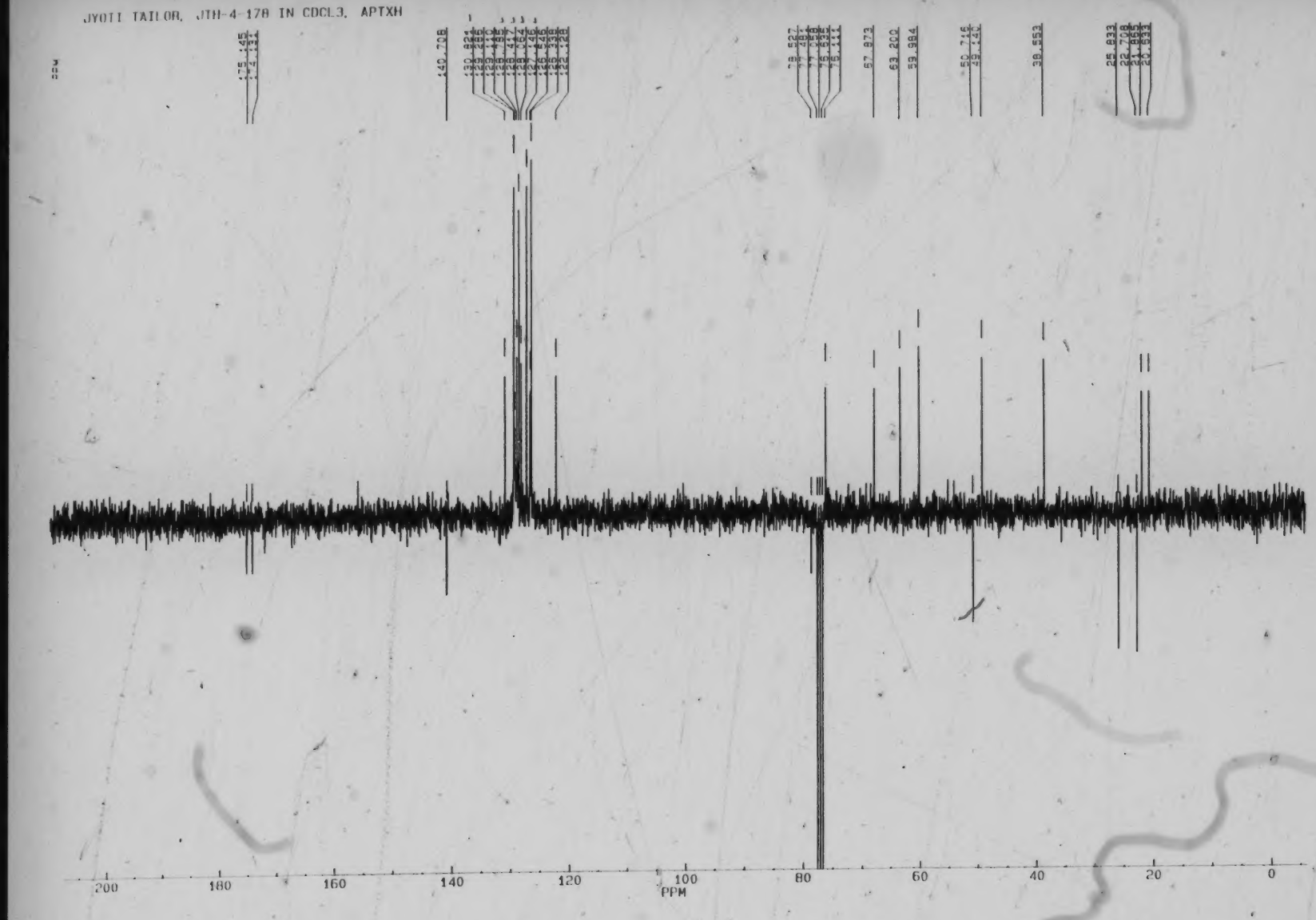
D1 2.0000000
S2 1
P9 1
D2 0
P0 1
D3 0
P6 1
D4 .0001000
RD 0.0
PW 0.0
DE 31.30
NS 2095
DS 2

O
NPh
Ph
N
O
OH
N
C(OMe)Me2

67b


9
8
7
6
5
4
3
2
1
ppm
30.46
1.06
1.00
0.91
1.09
1.25
1.10
1.72
6.52
3.67
2.61
1.76
4.63
3.57
16.17

137



BRUKER

AP270F.102
AU PROG:
X25.AU
DATE 6-6-0
TIME 19:33

SF 75.469
SY 112.0
O1 7000.000
SI 32768
TD 32768
SW 22727.273
HZ/PT 1.387

PW 0.0
RD 0.0
AQ .721
RG 800
NS 5200
TE 297

FW 28500
O2 4425.000
DP 18H CPD

LB 1.200
GB .010
CX 36.00
CY 10.00
F1 210.007P
F2 -5.984P
HZ/CM 452.793
PPM/CM 6.000
SR -1408.22

D1 .500
S1 18H
P9 100
D2 .0010000
S2 18H
P0 1.60
D3 .0070000
P6 8.40
D4 .0001000
RGA
RD 0.0
PW 0.0
DE 30.00
NS 5200
DS 2

138